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Abortive Epidemic Hepatitis.

By

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(Submitted for publication July 7, 1953.)

Many of the common epidemic diseases are known to occur in subclinical or abortive forms. In some of them the occurrence of such forms can be established by specific bacteriological or serological tests. In other diseases subclinical infections are likely in view of clinical or epidemiological observations.

There is nothing to suggest that epidemic hepatitis (H. E.) is exceptional in this respect, though the lack of specific tests — for general use, at least — leaves us comparatively ignorant of any abortive form.

Clinically, one may differentiate between two types of H. E. — icteric and anicteric. The diagnosis is based on the clinical symptoms, in conjunction with »liver-function» tests. None of these latter tests is specific for H. E., and many of them not even for inflammatory liver diseases. However, diagnosis of icteric cases is not difficult during epidemics. Anicteric cases, on the other hand, are often more difficult to identify. To some extent at least, this accounts for the fact that the frequency of anicteric cases reported for various epidemics varies between such wide limits as 9—89 % (10, 17). Common to both these types of H. E. is that individual cases exhibit certain subjective as well as objective clinical symptoms, which may serve as guide for both the patient and the physician.

It is the absence of characteristic symptoms that distinguishes the abortive forms. Perhaps more important still is the fact that the patient usually does not feel really ill. If abortive H. E. really occurs, it must therefore be sought among the »healthy» section of an epidemic community. Despite the enormous literature dealing with H. E., these »healthy» persons have remarkably seldom been the subject of systematic investigation as regards the occurrence of abortive cases.

Gowen (6) has shown that among apparently healthy individuals in an epidemic community there are some with slightly increased bilirubin in the serum. Pollock (14) describes a series of 17 children from a nursery where hepatitis had been endemic for some time. During an observation period of three months he was able

to establish by means of frequent tests that five of the children had short bouts of bilirubinuria without accompanying clinical signs. Both these authors have emphasized that abortive H. E. probably does occur. Dueci (4) came to the same conclusion, basing his opinion on the results of thymol tests from 194 persons who had certainly been exposed to the risk of infection but showed no signs of the disease. Values higher than normal were recorded for 38.6 % of this material, whereas the figure for a control group not exposed to the risk of infection was 13 %. Lastly, it has been found that where H. E. was experimentally induced in volunteers, some of these exhibited biochemical disturbances like those of hepatitis, but without clinical symptoms (13).

Author's Investigations.

At the end of 1949 and beginning of 1950, several cases of clinically typical H. E. occurred among the staff of a bakery. In addition, there were both icteric and anic-

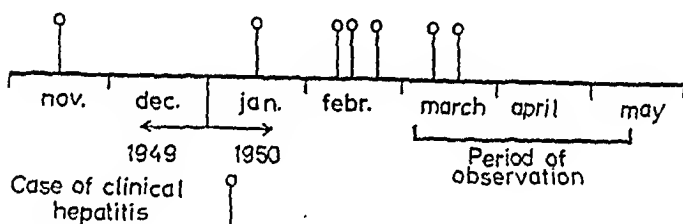


Fig. 1. The course of the epidemic. Time of onset of symptoms is marked for the clinical cases.

teric cases among the employees' families; etc. However, the investigation was confined to the bakery personnel, which comprised 41 persons to begin with. Altogether 7 of these became ill, 6 with jaundice and 1 without. The epidemiological findings showed that it was a question of contact infection — see Fig. 1. In no cases were the clinical symptoms severe; in most cases they were mild.

An investigation lasting more than two months was started on the 6th of March 1950, in an endeavour to find out whether abortive cases occurred. 2 of the 7 cases with clinically manifest H. E. developed during this period, so the epidemic was still in progress. The number of «healthy» working individuals was 34 — 27 men and 7 women — aged from 15 to 68 years. These 34 «healthy» persons were the subject of the investigation. Because of the local conditions, a thorough clinical examination was undertaken only when there seemed to be especially good reason for it. All 34 were interviewed on the occasion of each examination as to their subjective condition, with special reference to subjective symptoms suspect for H. E. An account of the laboratory technique is given in Table 1.

Discussion of the Laboratory Methods.

When these laboratory methods are applied to H. E. it is seen that there is a certain correlation between the degree of severity of the clinical picture of the disease and the extent of the pathological chemical disturbances — though not without

Table 1.

		Method	Value in
S e r u m	Bilirubin	Jendrassik & Gróf	mg %
	Direct reaction	Hijmans van den Bergh	+ or —
	Alk. phosphatase	King & Armstrong modif. acc. to Buch & Buch	Units
	Thymol turbidity	MacLagan	Ext. coeff.
	Zinesulphate turbidity	Kunkel	Ext. coeff.
	Cephalin-cholesterol.	Hanger	0 to 4 +
U r i n e	Bilirubin	Hammarsten	+ or —
	Urobilin	Schlesinger	+ or —
	Urobilinogen	Ehrlich	+ or —

exceptions. It could therefore be expected that the biochemical disturbances would be small in possible abortive cases, and therefore difficult to distinguish from technical errors. In order to avoid these sources of error as far as possible, all serum samples were taken in the morning on an empty stomach, and the urine tests were made on the morning urine. All analyses were carried out the same day, and by the same assistant. The whole series of cases was examined on at least three different occasions during the period of observation.

It is obvious that in such an investigation as this the emphasis will be laid on the laboratory results and the interpretation of them. The following considerations have been taken as a guide in this connection. As already pointed out, there are no specific laboratory tests for H. E.; but certain combinations of chemical disturbances may be said to be characteristic of the disease. These disturbances are liable to large variations, as regards the stage of the disease at which they occur, the duration (14, 19), and the magnitude. A single chemical finding may therefore be very difficult to interpret, or it may even be impossible to conclude anything. This is particularly so when the finding cannot be related to clinical symptoms.

In judging a quantitative laboratory value, the physician is often confronted with the problem of what is normal or otherwise in the individual case. There are of course accepted normal limits based on the results of examinations of a large number of normal cases. Amongst other things, the spread of the normal figures has to be taken into account in the statistical treatment of results, and for this reason no diagnostic conclusions can be drawn where the divergence is small. Ideally, one would wish to know the individual normal value for each patient under various conditions.

Repeated examinations during a long observation period may be very valuable in this connection. It is then possible to detect any progressive change. It is also

possible to obtain information about the individual normal value, either at the commencement of the investigation or at the end. Every deviation from this value must have its cause. From the point of view of the diagnosis, it is of minor importance whether this deviation attains or exceeds the generally accepted normal limits. It seems possible to make the method more sensitive in this way.

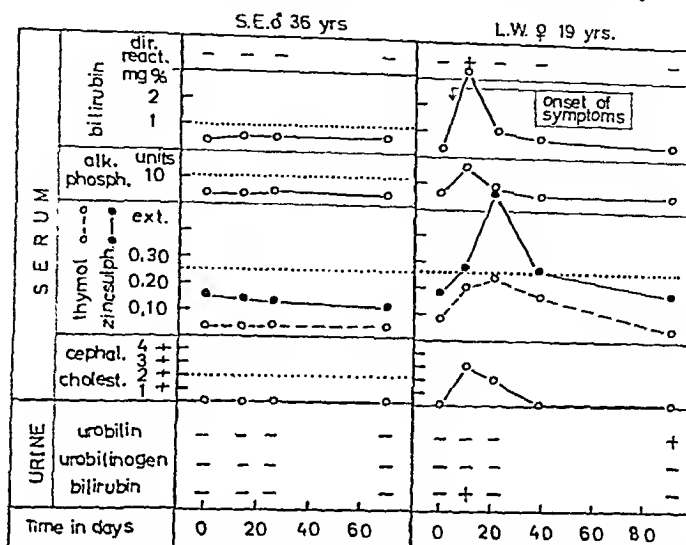


Fig. 2. Normal case (group A). Commonly accepted upper normal limits marked with dotted lines.

Fig. 3. Clinical hepatitis with jaundice.

As regards the diagnosis of abortive cases, the above considerations are of special importance in assessing the results of thymol and zinc sulphate turbidity tests. This point is illustrated by a clinically typical icteric case from the epidemic previously mentioned (fig. 3). The patient was subjectively healthy when the first tests were made. She became ill 4 days later with nausea, vomiting, slight catarrhal symptoms in the upper respiratory tract, and fever which soon abated. Liver palpable and somewhat tender. It will be seen from the diagram that the thymol curve does not attain the accepted upper normal limit (dotted line) (18). But in view of the low initial and final values, the intermediate values must be considered clearly pathological for this patient, though themselves low. The diagram also illustrates the diagnostic advantage of several different laboratory tests.

Results.

Two persons developed H. E. with jaundice during the period of observation. Among the remaining »healthy» individuals, neither the history nor the clinical examination — where such was carried out — provided any sure evidence of mild H. E. All of them considered themselves healthy and fit for work.

Thus the laboratory results are the sole basis for classification of the case material. This may be divided into three groups:

A. 24 cases. All analytical results normal, and, as regards the quantitative tests, no significant changes between the different examinations. (Example, Fig. 2.) In 19 cases urobilin was found in the urine on one single occasion, but no importance has been attached to this.

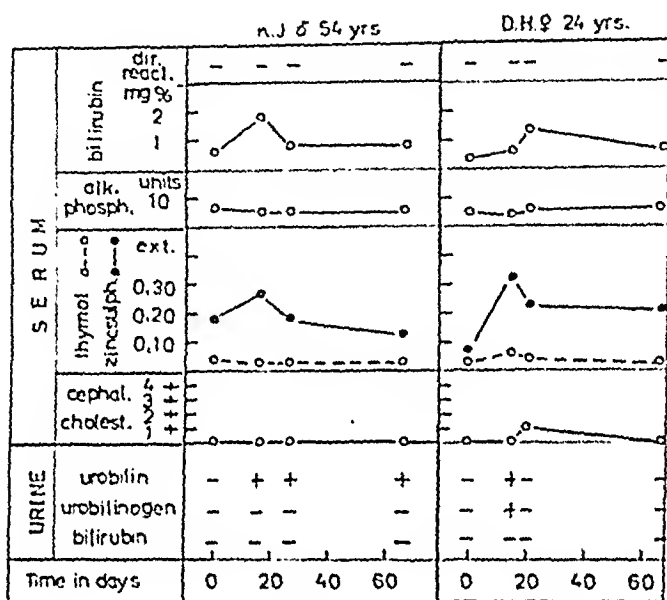


Fig. 4.

Fig. 5.

B. 5 cases. This group includes all cases with urobilinuria and urobilinogenuria at two or more examinations. On isolated occasions, a slight disturbance in one of the serum reactions was also noted. Although the changes were pathological, they did not justify any definite conclusions.

C. 5 cases (Figs. 4—8). The qualitative urine analyses and the curves giving the results of the blood-chemical analyses indicate significant disturbances in at least three independent liver functions.

Discussion.

These results thus show that among 34 persons, apparently healthy and fit for work, but living in an epidemic community there were 5 who showed abnormalities in the urine and blood chemistry. These abnormalities were of the same nature as those found in clinically established cases of H. E. But as regards the quantitative methods, the changes are less pronounced than those usually considered significant in laboratory diagnosis. Nevertheless, in the author's opinion, as already mentioned, no valid objection to the diagnostic value of the results can be made on this basis.

An aetiological foundation for these changes may reasonably be expected. The simplest explanation is that a subclinical or abortive form of H. E. was present.

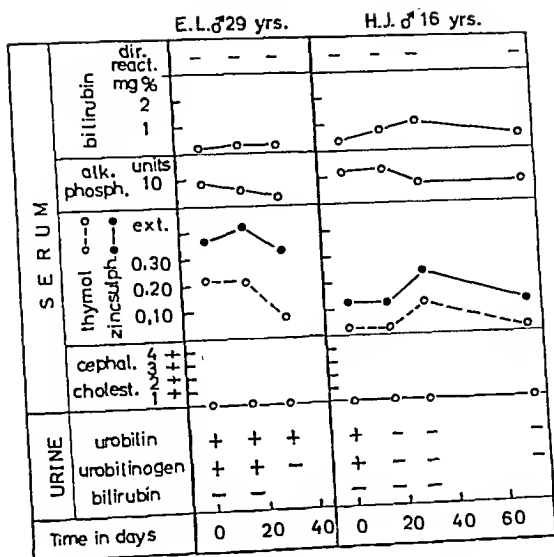


Fig. 6.

Fig. 7.

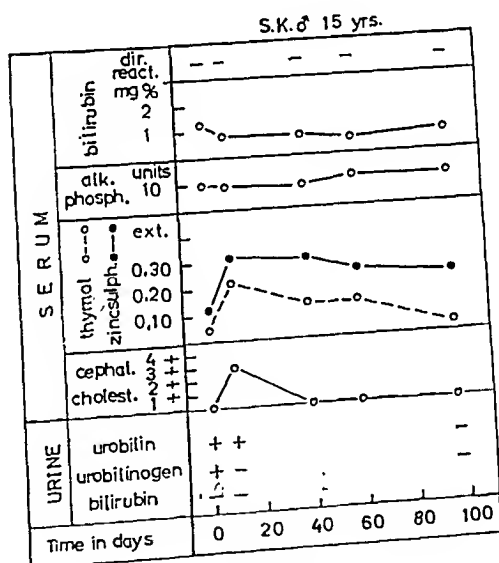


Fig. 8.

Fig. 4-8 Cases with abortive hepatitis (group C).

It has already been pointed out, however, that none of the tests used is specific for H. E. Similar chemical disturbances have been observed in other infectious diseases, of which infectious mononucleosis is probably the most well known. Such an origin is extremely unlikely, however, in view of the epidemiological situation. As a matter of fact, particular attention was paid to the possible occurrence

of other infectious diseases. The incidence of mild infections of the upper respiratory tract was noticeably high among the bakery staff. This was not at all surprising, in view of the time of year and widespread «colds» in the town. No less than 45 % of groups A and B had catarrhal symptoms at one or other of the examinations. Similar symptoms were observed in 3 of the 5 cases in group C. It therefore seems unlikely that the laboratory findings in group C could be explained by infections

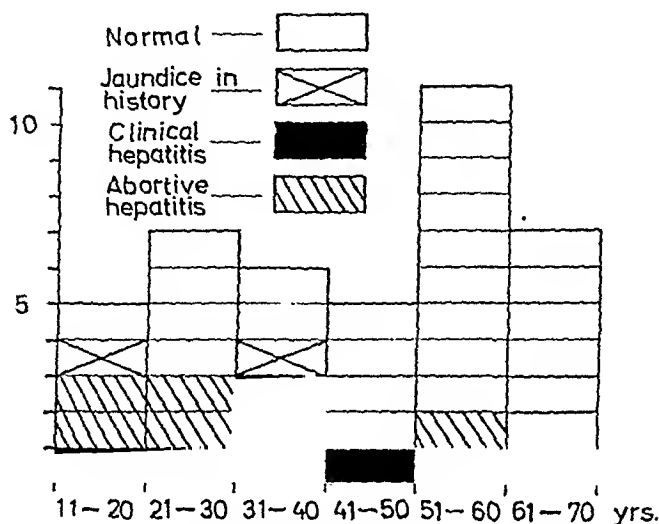


Fig. 9. The whole series of cases, including cases with clinical hepatitis, divided into different age groups.

of the upper respiratory tract. If that were so, the same chemical changes should have been found on a wider scale in groups A and B — *i. e.* group C would have been larger.

It seems most probable that the five persons in group C had H. E. without definite symptoms and physical signs — abortive H. E. In all probability they would not have been diagnosed without the above procedure.

Clinical and Epidemiological Aspects of Abortive Hepatitis.

In addition to the investigations referred to introductory, work by Drake et al. (5) also supports the above view. A large number of children in a boarding school where infectious hepatitis had long been endemic were examined twice, with one year's interval, with a skin test (8) developed by this research group. It was found that several of the children had different reactions on successive occasions, which, according to the theoretical basis of the test, indicated that they had acquired antibodies against the hepatitis virus. These children had not shown signs of illness in the intervening year, however, and it was therefore suggested that they might have had a subclinical form of infectious hepatitis.

It may seem remarkable that any form of hepatitis could manifest no clinical symptoms, as was the case with group C. Clinical experience shows that bodily

exertion aggravates the disease, a circumstance which has even been utilised diagnostically by Baker et al. in provocative exercise tests (2). It should be noted that in only one of the 5 abortive cases (S. K.) was the patient advised not to continue working and to rest. This was after the second series of tests had been taken, when the laboratory results were considered to be such definite evidence that there could be no doubt about the diagnosis. The fact that the patient protested and thought it unnecessary to stop working only confirms the lack of sufficiently alarming subjective symptoms in abortive cases. The other four continued working as usual the whole time, apparently without demonstrable disability. The mild clinical course of the illness was therefore not due to early treatment.

As already mentioned, each worker was asked at each examination about subjective symptoms suspect as regards H. E. These questions yielded practically nothing. Any discomfort that had occurred was either quite irrelevant or so slight, brief and uncharacteristic that the most it allowed was a faint doubt about the aetiological background. In order to investigate this further, the histories of the five abortive cases were checked once more. The value of information obtained in this way is of course disputable, but it may have some significance in this connection.

Catarrh in upper respiratory tract.....	3 (S. K., H. J., E. L.)
Dyspepsia	2 (S. K., D. H.)
Tiredness	2 (S. K., D. H.)
»Nothing to speak of»	1 (K. J.)

Among the many symptoms of manifest H. E., catarrh in the bronchi and upper respiratory tract are fairly often observed, particularly in the prodromal stage (10). In another group of cases treated in this clinic, such symptoms were observed in 6 % of the cases. Whether or not these symptoms are to be ascribed to the hepatitis virus has not yet been discussed as far as I know, but it appears to be generally assumed that such is the case. The high incidence of catarrh in groups A and B, which showed no chemical signs of H. E., suggest that the catarrhal symptoms among the abortive cases were not necessarily due to the hepatitis virus, but rather that it was a question of the coincidence of two different diseases.

Experience of clinically typical cases of H. E. shows that a secondary infection may considerably aggravate the primary disease, the hepatitis. When catarrhal symptoms are observed in H. E., it seems likely that they are attributable to an infection other than the hepatitis. They may rather be looked upon as evidence of a complicating disease which requires special treatment if such is possible. It may be that the inconsistent results reported for the treatment of H. E. with antibiotics can to some extent be explained against the background of these considerations.

Symptoms affecting the digestive tract were not noteworthy in any way, apart from the fact that they were so mild and transient that in no case was much attention paid to them. In case S. K., there was in addition a suspect tender region above the liver. D. H. had diarrhoea twice.

Case D. H. is of particular interest in that she felt tired. In spite of the fact that

she was well aware of the investigation's purpose, she did not say anything about this, because she thought that tiredness was quite irrelevant. At the end of the investigation, it was found that she had in the meantime visited the out-patient department. Liver function tests were carried out there, and the results were much the same as those in the diagram for the third examination. It was of course impossible to draw any conclusions about the laboratory results from a single examination, and the diagnosis made was neurasthenia. This accords with her subjective symptoms, but it throws no light on the aetiological background. It is not at all improbable that this patient represents a type of H. E. occurring in an epidemic community, which is not really unusual but commonly overlooked.

Although the series is small, it is of interest to consider the incidence of the disease in the different age groups. Fig. 9 shows that both the manifest and abortive H. E. affected in particular the younger people in this epidemic. If the cases are divided into two categories at 40 yrs., there is a difference between the incidence of both forms together in the two categories of $37 \pm 14.7\%$, which is statistically probable, with $P = 0.01$. If only abortive cases are considered, the corresponding figure is $24 \pm 12\%$, $P = 0.05$. (P denotes the probability that the difference in question may be due to random variations.) Since the investigation of abortive cases only dealt with the latest third of the supposed total length of the epidemic, it is conceivable that abortive cases had occurred at an earlier stage, but had recovered, and therefore remained undetected. The above calculations suggest, however, that if such were the case, it would not change the age distribution to any great extent.

It is a well known fact that H. E. morbidity is usually greater in the younger age groups. Exceptions to this rule have been observed, where the sickness rate among older persons has been high, and often associated with a higher mortality, especially among women. The discrepancy is sometimes so marked that it has even been suggested that an altogether different form of the disease may be involved (1, 11, 15, 16). A certain correlation has been noticed between the length of an epidemic and the high morbidity among older persons (15).

There are of course many factors which contribute to the duration of an epidemic. Besides variations in the virulence of the infecting agent etc., another important factor is the degree of immunity in the group affected. It is generally true that an epidemic becomes much more widespread in all age groups when it affects a population not previously in contact with it. H. E. appears to be no exception in this respect, and there are circumstances which favour such an explanation of epidemics with exceptional age incidence (16).

H. E. has been a common disease in this district for decades. The age distribution in the small epidemic considered here is natural under such circumstances. Furthermore, in view of clinical experience that H. E. is usually milder in younger persons, it is not surprising that abortive cases are most common in this age group.

Earlier investigations of the age distribution in hepatitis epidemics have been based on clinically manifest cases. Nothing was known about abortive cases in this respect. The results of the present investigation indicate that, where a lower

morbidity is observed among older persons, this is real, not apparent, and depends on a higher incidence of undiagnosed abortive cases among older people. This conclusion assumes, of course, that the biochemical reaction to the disease does not change with increasing age. The author has not been able to find anything which suggests such a change, neither in the literature nor in experience derived from the laboratory technique used in this investigation.

Thus everything suggests that in districts where H. E. has occurred frequently, susceptibility to the disease is smaller in the higher age groups. The most obvious explanation of this is that there is under such conditions a fairly widespread immunity as a result of previous affection by the disease. Among the 29 healthy persons in the present series, there were only 2 — their ages 19 and 40 — who had previously had an icteric disorder with symptoms anamnesticly like those of H. E., though not associated with any known source of infection (see Fig. 9). How the others had acquired their resistance is not clear. It seems that many of them might unknowingly have had an abortive form of H. E. when younger, which had rendered them to some extent immune. There has been no lack of opportunities for this. If the proportion of abortive to manifest cases observed in the present investigation is in any way representative, it is obvious that the abortive form may be remarkably common, which provides further support for the hypothesis advanced.

The lack of specific diagnostic methods may make the diagnosis of hepatitis difficult from the aetiological point of view. In the individual case, it may be impossible to distinguish with any certainty between H. E., homologous serum hepatitis (and »sporadic hepatitis») solely on the basis of the clinical symptoms and the liver-function tests known hitherto. Information gained from the history about possible sources of infection may be of very great value in such circumstances. A non-selected group of 100 patients who were treated at the clinic for »acute infectious hepatitis» were interviewed on this point, not only when they entered hospital but also after they had left. 55 % were able to recall some possible source of infection, either in the form of other cases in the family or more generally because they had been in districts where H. E. was known to occur. In 19 % of the cases there was possibly a question of homologous serum hepatitis. In the remaining cases, 26 %, neither of these possibilities were present. In this connection, it may be pointed out that abortive cases might be completely untraceable spreaders of infection. The importance of a thorough case history, and perhaps to an even greater extent, of up-to-date information on relevant epidemics, is evident here. These latter comments are perhaps worth the consideration of blood-donor organisations, whose donors belong to the age groups where abortive cases seem to be most common.

Nothing is known about the prognosis of abortive H. E., of course. It is likely to heal without residue. But it is known that H. E. may be transformed to a chronic form, with a clinically inapparent intermediate stage of long duration — cf. Bloomfield (10). It is therefore impossible to disregard H. E. in the aetiology of liver cirrhosis merely on the grounds of a negative history regarding previous affection by H. E. Information that the patient has at some time or other been in epidemic surroundings is sufficient to imply that this possibility must be taken into consideration.

Summary.

On analogy with epidemic diseases in general, it is assumed that epidemic hepatitis (H. E.) may also occur in abortive forms. Certain previous investigations indicate that such is the case.

The absence of distinctive clinical symptoms and of specific tests for H. E. make the diagnosis of abortive H. E. difficult, so that it is necessary to rely on laboratory methods. The laboratory technique used (Table 1) is discussed, and the importance of repeated examinations over a fairly long period of observation is stressed. The method thus becomes more sensitive, and even small changes in the blood chemistry can then be assigned diagnostic significance.

Chemical changes were observed in 5 out of 34 apparently healthy persons in epidemic surroundings. These changes were of the same type as are observed in H. E. The aetiology is discussed, and the most probable explanation seems to be that abortive H. E. was present.

The subjective symptoms exhibited by the abortive cases were particularly insignificant and uncharacteristic, and of no diagnostic value. Slight nasal catarrh was observed in three cases. There is reason to suppose that these were due to accidental coincidence of two different diseases. The significance of this is discussed.

The limited case material available suggests that abortive cases may be relatively common in an epidemic environment. It is statistically probable that this form of the disease is more common at ages less than 40. This fact is discussed from immunological and epidemiological points of view. The part played by abortive cases as uncontrollable spreaders of infection is obvious — a circumstance which is worthy the attention of blood-donor organisations. The importance of up-to-date knowledge of the epidemiological situation is stressed.

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References.

1. Alstedt, G.: *Amer. J. Med. Sc.* 213, 257 (1947). — 2. Baker, M. H., Capps, R. B., Allen, F. W.: *J. A. M. A.* 129, 653 (1945). — 3. Björneboe, M.: *Liver Disease*, Ciba Foundation Symposium, London 1951. — 4. Ducci, H.: *Ibid.* — 5. Drake, M. E., Ward, Ch., Stokes J., Jr., Henle, W., Mediar, G., Mangold, F., Henle, G.: *J. Exp. Med.* 95, 231 (1952). — 6. Gowen, G. H.: *Bull. U. S. Army Med. Dpt.* 84, 41 (1945) cit. 10. — 7. Hardy, H. L., Feenster, R.: *New Engl. J. Med.* 235, 147 (1946). — 8. Henle, G., Drake, M. E., Henle, W., Stokes, J., Jr.: *Proc. Soc. Exper. Biol. & Med.* 73, 603 (1950). — 9. Kunkel, H., Hoagland, Ch.: *Ibid.* 236, 891 (1947). — 10. Lichtman, S. S.: *Diseases of The Liver, Gallbladder and Bile Ducts*, Philadelphia 1949. — 11. Müller, Th.: *Schweiz. Med. Wchsehr.*

77, 796 (1947). — 12. Mc.Nee, J. W., Liver Disease, Ciba Foundation Symposium, London 1951. — 13. Neefe, J. R., Stokes, J., Jr., Reinhold, J. G., Lukens, F. D.: J. Clin. Invest. 23, 836 (1944). — 14. Pollock, M. R.: Brit. Med. J., 2, 598 (1945). — 15. Ryssing, E.: Ugeskr. f. Læg. 110, 1099 (1948). — 16. Stokes, J. Jr.: Liver Disease, Ciba Foundation Symposium, London 1951. — 17. Sundell, C.-G.: Sv. Läkartidn. 46, 2133 (1949). — 18. Tallroth, A.: Acta. Chir. Scand. Suppl. 145 (1949).

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The Cytology of the Bone Marrow in Pernicious Anæmia with Normal Hæmoglobin Level.

Glossitis and Subacute Combined Degeneration of the Spinal Cord due to Deficiency of the Anti-Pernicious-Anæmia Principle.¹

By

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This paper is a report on a series of patients with chronic glossitis and/or subacute combined degeneration of the spinal cord, but with normal hæmoglobin levels. It is the purpose of this study to present evidence showing that such cases may be due to deficiency of the anti-pernicious-anæmia factor, and that this type of pernicious anæmia is often allowed to pass unrecognized. It is shown that even though the hæmoglobin level is normal, signs of pernicious anæmia may be present in the peripheral blood; and, in particular, the importance of bone-marrow examinations in such cases is emphasized.

Both glossitis and subacute combined degeneration of the spinal cord may be very conspicuous and troublesome manifestations in pernicious anæmia. It is often emphasized in the standard textbooks that both glossitis and neurological symptoms may occur very early in the disease at a time when there is little or no anæmia (Whitby and Britton, Wintrobe). However, it is difficult, when the hæmoglobin level is normal, to definitely establish that cases of glossitis or subacute combined degeneration of the cord are due to deficiency of the anti-pernicious-anæmia factor, which in turn entails some uncertainty as to whether anti-pernicious-anæmia treatment should be instituted.

If the manifestations mentioned were merely precursors of pernicious anæmia, the safest course would be to await manifest blood changes before specific therapy is instituted. However, in some cases both glossitis and neurological symptoms

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may persist for several years (in the present series up to 15 years) without the development of a frank pernicious anæmia. In such cases it would be of value if evidence were available suggesting that the condition was due to deficiency of the anti-pernicious-anæmia factor in spite of a normal hæmoglobin level. In the cases reported below slight changes in the peripheral blood were certainly present, but they were so inconspicuous that a definite diagnosis of pernicious anæmia could not be made. However, in spite of a normocytic erythropoiesis bone-marrow examinations revealed the presence of »pernicious-anæmia neutrophils», which was suggestive of deficiency of the anti-pernicious-anæmia factor. Judging from the literature, it seems as if sufficient attention has not been paid to the fact that perniciosiform maturation disturbances may occur as an isolated phenomenon in the granulopoiesis, thus suggesting that a glossitis or subacute combined degeneration with normal hæmoglobin level may be attributable to deficiency of the anti-pernicious-anæmia factor.

Methods.

The hæmoglobin determinations were made with a photo-electric hæmoglobino-meter in six cases and with Sicca's hæmoglobinometer in two cases. The hæmoglobinometers were standardized so that 100 % was equivalent to a hæmoglobin content of 14.8 grammes per 100 ml of blood. Enumerations of erythrocytes were carried out in the Bürger-Türk counting chamber. All determinations were made in duplicate or in quadruplicate. The hæmoglobin content of the erythrocytes was expressed by the colour index calculated as follows:

$$\frac{\text{Hæmoglobin percentage}}{\text{Erythrocytes} \times 21}$$

The bone marrow was studied in smears stained by the May-Grünwald-Giemsa method. In every sample, the content of pernicious-anæmia cells was estimated by counting 500 cells both from the red cell and the neutrophil series.

Gastric secretion was studied after histamine stimulation in seven cases and after insulin stimulation in one case. Only cases showing achlorhydria were included, as it must be regarded as uncertain whether cases of essential pernicious anæmia may have acid secretion.

Gastric biopsy as proposed by Doig et al. was not performed. However, it should be mentioned that in fragments of gastric mucosa secured through a gastroscope these authors demonstrated the same histological changes as are seen in pernicious anæmia in patients with neurological symptoms but without significant hæmatological signs of this disease.

Report of Cases.

Case 1. A woman (M. H. 384/50), aged 61, had for the last 12 months had progressive paræsthesiæ of the hands and feet and a sensation of numbness in the two ulnar fingers on both sides. During the same period she had also suffered from intense pain and burning in the tongue and oral mucosa.

Physical examination. The tongue was red and smooth; there were fissures at the angles of the mouth.



Fig. 1.



Fig. 2.

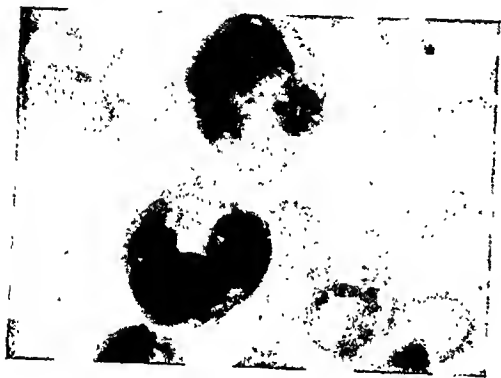


Fig. 3.

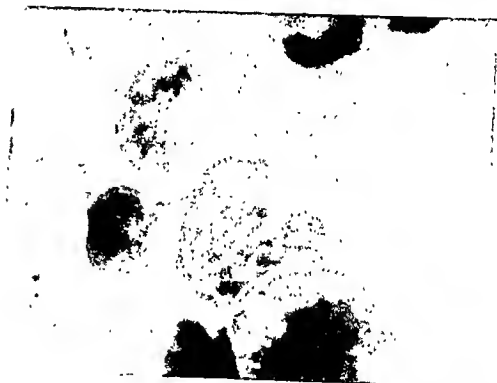


Fig. 4.

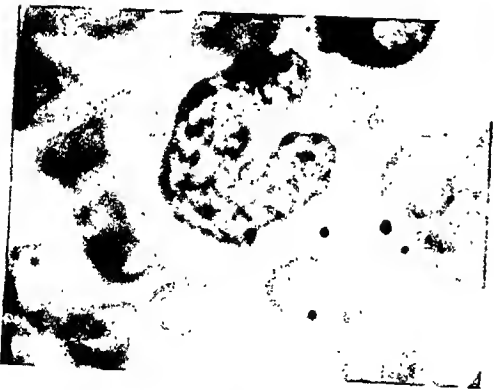


Fig. 5.

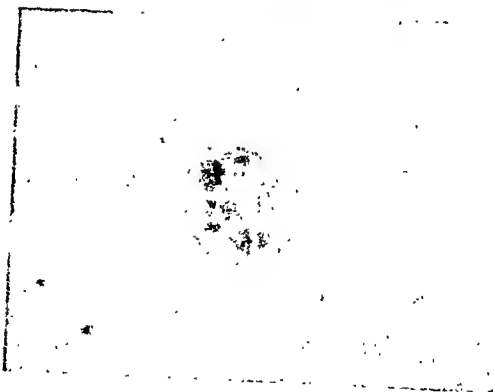
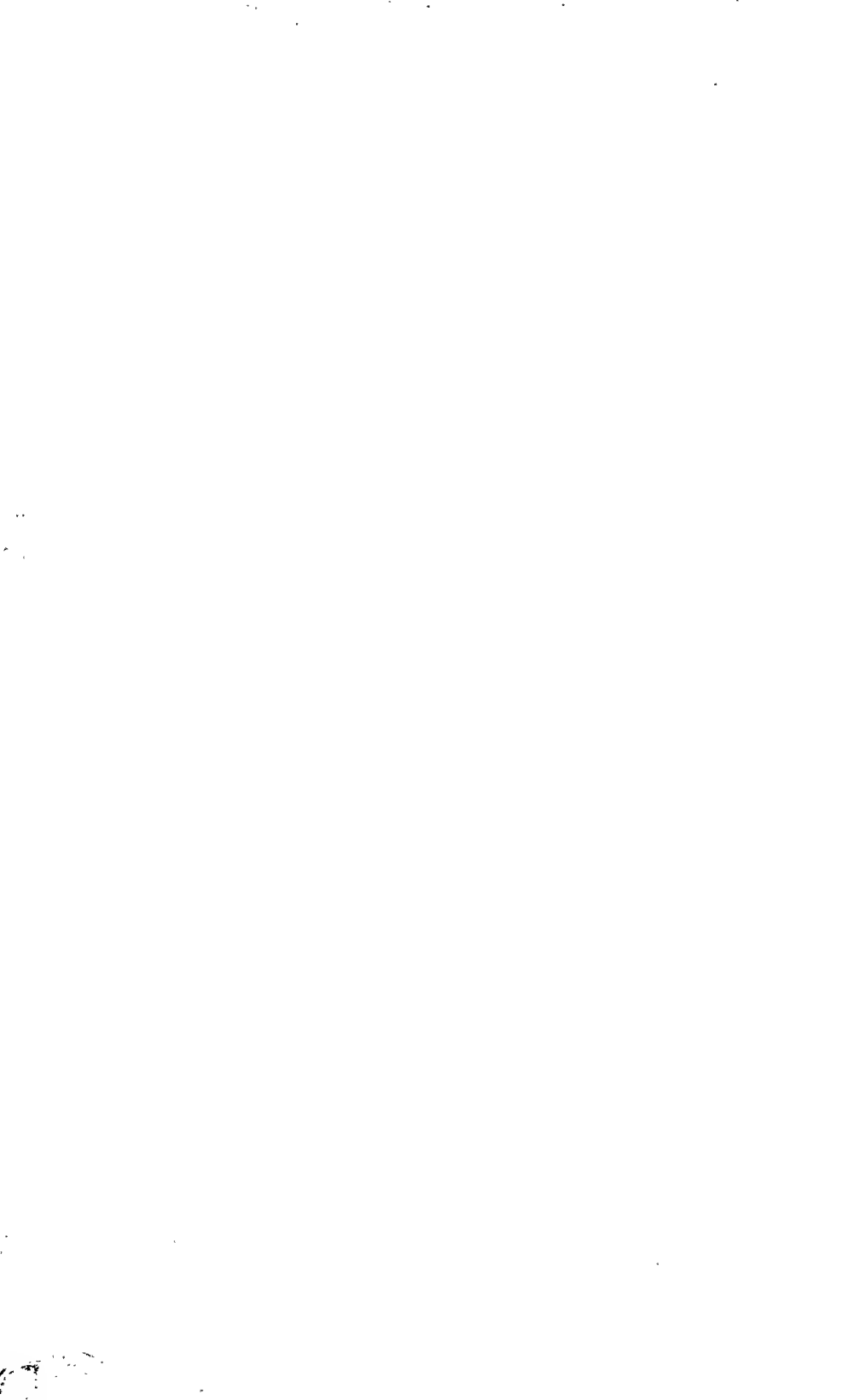


Fig. 6.

Figs. 1—6: «Pernicious-anæmia neutrophils» of the bone marrow in cases of glossitis and neuropathy with normal hæmoglobin level. Figs. 1 and 2. Giant metamyelocytes. Figs. 3—5. Giant stab cells. Fig. 6. Macropolycyte. $\times 1,000$.

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The finger-nose test revealed distinct ataxia of the upper extremities; the deep reflexes were hyperactive. The knee-heel test showed ataxia of the lower extremities; the ankle and knee jerks were weak; Babinski's phenomenon was absent. The gait was slightly unsteady.

Laboratory findings. The spinal fluid showed 1 cell per cu.mm, normal protein content (Bisgaard 10), and a negative Pandy reaction. The Wassermann reaction in blood and spinal fluid was negative. Histamine-fast achlorhydria was demonstrated.

Blood examination showed hæmoglobin 85 % (12.6 g), erythrocytes 3,580,000, colour index 1.13, leucocytes 6,300, normal smear, reticulocytes 5 per thousand.

The bone marrow revealed a normocytic erythropoiesis. In the granulopoiesis some large promyelocytes and myelocytes with irregular, often lobulated nuclei were observed. The megakaryocytes were normal.

Treatment and course. Intramuscular injections of liver extract (Hepsol MCO) were given, 5 ml every other day for three days, followed by 5 ml every fortnight. Following the treatment a slight increase in the hæmoglobin level and a marked increase in the erythrocyte count were observed, and the colour index became normal. Three weeks after the institution of liver therapy the values were: hæmoglobin 92 % (13.6 g), erythrocytes 4,580,000, colour index 0.96. The symptoms from the oral mucosa were also considerably improved. The tingling and numbness in the extremities remained unchanged, whereas the general condition improved.

A blood examination one year later (when the patient had been without anti-pernicious-anæmia treatment for two months) showed hæmoglobin 97 % (14.4 g), erythrocytes 4,530,000, colour index 1.02, leucocytes 5,200, normal smear. *The bone marrow* showed some large myelocytes with irregular nuclei; there were also a few typical giant stab cells. The erythropoiesis was normocytic, and the megakaryocytes were normal. — The patient complained of intense pain in the tongue; after resumption of liver therapy this symptom abated and the bone marrow returned to normal.

Two years after the institution of the treatment the condition was unchanged. Blood and bone-marrow examinations showed normal values.

Case 2. A woman (M. H. 1872/51), aged 68, had for six months suffered from fatigue, lassitude, and pain and burning in the tongue. She had consulted a laryngologist, who had painted the tongue with a silver-nitrate solution without any beneficial effect. Injections of nicotinic acid had also proved ineffective.

Physical examination. Nothing abnormal was noted. The colour of the tongue was normal. The neurological examination was also non-contributory.

Laboratory findings. Histamine-fast achlorhydria was demonstrated. Blood examination showed hæmoglobin 87 % (12.9 g), erythrocytes 3,800,000, colour index 1.10, leucocytes 7,500, normal smear. *The bone marrow* showed normocytic erythropoiesis. In 7 % of the cells of the myeloid series slight perniciosiform maturation disturbances in the form of giant metamyelocytes and giant stab cells were observed.

Treatment and course. Intramuscular injections of vitamin B₁₂, 0.100 mg twice weekly, were given for a fortnight. At the end of the course the pain in the tongue had disappeared and the fatigue had abated, resulting in an improvement of the general health. The bone marrow now showed normal conditions; hæmoglobin 89 % (13.2 g), erythrocytes 4,230,000, colour index 1.00. A maintenance course of 0.050 mg of vitamin B₁₂ once weekly was instituted. At a follow-up examination six months later there was no return of lingual symptoms.

Case 3. A woman (M. H. 517/52), aged 42, had for 15 years suffered from pain and burning in the tongue. The pain had varied in intensity, but had often been very troublesome. Only for very brief periods (a couple of days at a time) had the lingual symptoms been absent. During the last three months prior to admission the pain in the tongue had been constantly present and more troublesome than ever before.

For 15 years she had also suffered from numbness in the tips of the fingers, the knees and the soles of the feet, excessive sensitiveness of the lateral side of the right leg, and tingling of both lower extremities, right from the groins to the tips of the toes. During the same period she had felt a certain weakness of the legs when she was walking, and sometimes her gait had been a little unsteady.

Physical examination. The tongue had a flame-like appearance, with alternating red and grey areas. There was some papillary atrophy.

Neurologically, the upper extremities were normal. The knee and ankle jerks were absent; the plantar reflexes were normal. There was a tendency to sway in the Romberg test. The lower extremities were slightly hypotonic, but muscular power was normal. The gait was a little cautious but otherwise normal.

Laboratory findings. The spinal fluid showed 2 cells per cu.mm, normal protein content (Bisgaard 10), and a negative Pandy reaction. The Wassermann reaction in blood and spinal fluid was negative. Histamine-fast achlorhydria was demonstrated.

Blood examination showed hæmoglobin 89 % (13.2 g), erythrocytes 3,480,000, colour index 1.22, leucocytes 4,900, normal smear, reticulocytes 10 per thousand, thrombocytes 200,000, serum iron 0.232 mg%.

The bone marrow revealed a mainly normocytic erythropoiesis, yet with a few intermediate megaloblasts. In the granulopoiesis there were pronounced maturation disturbances in the form of giant metamyelocytes, giant stab cells and macropolycytes. The megakaryocytes were normal.

Treatment and course. Intramuscular injections of potent liver extract (Hepsol Fortior MCO), 5 ml, and vitamin B₁₂, 0.045 mg, were given daily for three days, followed by oral administration of desiccated hog's stomach (Pylorin MCO, 5 g daily) and intramuscular injections of Hepsol Fortior, 5 ml, twice a week. Three days after the institution of treatment the pain in the tongue diminished, and after a week it had completely disappeared. The sense of taste was normal, and the patient could eat all sorts of food without discomfort.

After anti-pernicious-anæmia treatment for three weeks the tongue appeared completely normal; there was no papillary atrophy. The abnormal sensations in the extremities were still pronounced and troublesome. At a neurological examination then performed the condition was quite unchanged in that respect. Blood examination showed hæmoglobin 87 % (12.9 g), erythrocytes 3,870,000, colour index 1.07, leucocytes 4,280, normal smear. The bone marrow was perfectly normal with normocytic erythropoiesis and normal granulopoiesis without perniciosiform maturation disturbances. At a follow-up examination three months later the patient was still free from lingual symptoms and there were no signs of glossitis; the neurological manifestation was unchanged. Blood examination showed hæmoglobin 87 % (12.9), erythrocytes 4,470,000, colour index 0.98; the bone marrow picture had returned to normal. One year later the condition was unchanged.

Case 4. A woman (M. H. 828/52), aged 71, was admitted to the hospital with a complaint of soreness of the tongue.

At the age of 65 she had been admitted to the Department of Neurology for headache, which had been attributed to hypertensive encephalopathy. Before that time she had for three years suffered from intense pain and burning in the tongue, which had often been fiercely red. She had repeatedly consulted a laryngologist. Furthermore, for about two years she had had tingling of the fingers and toes.

Physical examination. The tongue was red and smooth. The neurological examination did not reveal any abnormalities.

Laboratory findings. Histamine-fast achlorhydria was demonstrated. The spinal fluid was normal. The Wassermann reaction in blood and spinal fluid was negative. Blood pressure 200/105; hæmoglobin 92 % (13.6 g), erythrocytes 3,300,000, colour index 1.33, volume index 1.57, leucocytes 6,300. The bone marrow revealed a mainly normocytic

erythropoiesis, yet with a few intermediate megaloblasts. In the granulopoiesis there were distinct maturation disturbances in the form of giant metamyelocytes, giant stab cells and macropolycytes. The megakaryocytes were normal.

Treatment and course. The pain in the tongue disappeared during treatment with liver injections (Hepsol Fortior), and the paræsthesiæ diminished. A slight increase in the reticulocytes (maximum 6 %) occurred. A blood examination on the 12th day of treatment showed hæmoglobin 92 % (13.6 g), erythrocytes 3,310,000, colour index 1.31, volume index 1.4.

On discharge, maintenance liver therapy was instituted. One year later the patient was readmitted, this time for trigeminal neuralgia. On admission the blood findings were: hæmoglobin 90 % (13.3 g), erythrocytes 4,020,000, colour index 1.07. As anæmia had never been observed, liver therapy was discontinued. Two months later a bone-marrow examination revealed perniciosiform maturation disturbances in the granulopoiesis; the hæmoglobin level was unchanged, but soreness of the tongue had returned. After resumption of liver therapy the lingual pain disappeared and the bone-marrow picture returned to normal.

For the next year the patient received regular liver therapy and had no lingual discomfort. She was then again admitted to this hospital for trigeminal neuralgia. The tongue appeared normal. Blood examination showed hæmoglobin 95 % (14.0 g), erythrocytes 4,500,000, colour index 1.00. Liver therapy was stopped for one month without any resulting change in the hæmoglobin level, but soreness and redness of the tongue returned. These symptoms disappeared on resumption of liver therapy.

After that time liver therapy was given without interruption. Occasionally, soreness of the tongue developed but usually disappeared again when the dose of liver extract was increased for some time.

On the last admission to this hospital she had for three months had progressive pain and burning in the tongue although she had during this period received one weekly injection of purified liver extract (containing 50 U. S. P. units).

Physical examination. The tongue was red and smooth, with marked redness of the oral and faucial mucosæ. The neurological examination revealed ataxia in the finger-nose test and a positive Romberg sign. Blood examination showed hæmoglobin 92 % (13.6 g), erythrocytes 5,120,000, colour index 0.90.

Treatment and course. The liver therapy was continued but in larger dosage than before. The patient was given intramuscular injections of 50 units + vitamin B₁₂, 0.100 mg, daily for three days. A week later the soreness and redness of the tongue had disappeared and the papillary atrophy was less pronounced.

Case 5. A woman (D. N. 9369), aged 53, had shown achlorhydria 15 years previously. She had for periods suffered from hypochromic anæmia, which had been treated with iron preparations with good effect in another hospital. For about two years she had had pain in the tongue and numbness and tingling of the legs and feet, and during the last six months she had complained of weakness of the lower extremities with progressive unsteadiness of gait.

Physical examination. The tongue was very red with papillary atrophy.

There were moderately severe spastic paralysis and ataxia of the lower extremities, abolished sense of position, loss of vibration sense up to the iliac crests, and hypæsthesia gradually shading away on the abdomen. Knee jerks were weak and ankle jerks absent; bilateral Babinski's phenomenon was found. The patient was unable to walk unaided.

Laboratory findings. The spinal fluid showed 1 cell per c.mm., protein content just at the upper normal limit (Bisgaard 25), and a positive Pandy reaction. The Wassermann reaction in blood and spinal fluid was negative. Histamine-fast achlorhydria was demonstrated.

Blood examination showed hæmoglobin 90 % (13.3 g), erythrocytes 3,800,000, colour index 1.12, leucocytes 5,800, normal smear.

The bone marrow revealed a slight shift to the left in the erythropoiesis with some fairly large, basophilic normoblasts but no megaloblasts. In the granulopoiesis there were rather pronounced maturation disturbances in the form of giant metamyelocytes, giant stab cells and macropolycytes. The megakaryocytes were normal.

Treatment and course. The patient was given intramuscular injections of vitamin B₁₂, 0.015 mg daily for a fortnight, and at the same time walking and co-ordination exercises were instituted. During the anti-pernicious-anæmia treatment no increase in the reticulocytes was observed, but at the end of the course the erythrocyte count had increased to 4,200,000, whereas the hæmoglobin level was unchanged, 90 % (13.3 g), colour index 1.02. At that time there was no definite change in the neurological symptoms.

Two months after the discharge we were informed that during the first three weeks at home the gait had been improved but then returned to the former state. However, the lingual symptoms had completely disappeared. At that time the patient was still being given intramuscular injections of vitamin B₁₂, 0.015 mg twice a week. Two years later the condition was unchanged.

Case 6. A woman (E. S., born June 17, 1878), aged 74, had suffered from diabetes mellitus for 20 years, for which she had received insulin. During the last ten years she had occasionally suffered from soreness of the tongue, which during the last year had become progressive worse and been accompanied by an almost constant sensation of burning in the tongue. During the last year she had also been troubled by progressive numbness and tingling in the hands and fingers, and manual clumsiness had been present for two months. Both the lingual and neurological symptoms had previously been interpreted as being due to the diabetes.

Physical examination. In some areas the tongue was devoid of papillæ, but the colour was normal.

The neurological examination revealed loss of the finer co-ordination of the fingers. The knee jerks were absent, the plantar reflexes normal.

Laboratory findings. There was achlorhydria after insulin stimulation. Blood examination showed hæmoglobin 100 % (14.8 g), erythrocytes 3,570,000, colour index 1.33, leucocytes 5,700, normal smear, thrombocytes 350,000.

The bone marrow revealed a normocytic erythropoiesis; the megakaryocytes were normal. In the granulopoiesis there were maturation disturbances in the form of giant metamyelocytes and giant stab cells.

Treatment and course. Intramuscular injections of vitamin B₁₂, 0.060 mg daily for 10 days, followed by 0.060 mg every fortnight for 2 months. Thereafter vitamin B₁₂, 0.020 mg daily, + intrinsic factor (Bendogen GEA¹) were given orally.

After ten days the erythrocyte count had increased to 4,250,000, hæmoglobin 100 % (14.8 g), leucocytes 5,100, normal smear. The lingual symptoms had disappeared but the paræsthesiæ persisted.

At an examination after 4 months' treatment there were no papillary atrophy of the tongue or other lingual symptoms. The paræsthesiæ had abated; slight numbness and tingling in the hands and fingers were present only on rare occasions. There was no ataxia of the fingers. Blood examination showed hæmoglobin 100 % (14.8 g), erythrocytes 4,500,000, colour index 1.11, leucocytes 5,500. The bone marrow showed normal conditions. Twelve months after the institution of treatment the improvement was still maintained; hæmoglobin 96 % (14.2 g) erythrocytes 5,130,000.

Case 7. A woman (M. H. 21/53), aged 77, had for 2 years suffered from pain and burning in the tongue and numbness and tingling in the fingers and toes.

Physical examination. The tongue was fiercely red with atrophic papillæ. There were fissures at the angles of the mouth. The neurological examination did not reveal any abnormalities.

¹ Bendogen was generously supplied by the GEA Medicinal Laboratories, Copenhagen.

Laboratory findings. Histamine-fast achlorhydria was demonstrated. The Wassermann reaction was negative. Hæmoglobin 90 % (13.3 g), erythrocytes 3,140,000, colour index 1.36, leucocytes 5,080, normal smear, thrombocytes 362,000. The bone marrow showed normocytic erythropoiesis. The granulopoiesis showed some maturation disturbances in the form of giant metamyelocytes and giant stab cells.

Treatment and course. Intramuscular injections of liver extract (Hepsol Fortior MCO), 5 ml every other day, were given for a fortnight. At the end of that period the lingual symptoms had disappeared, the tongue had a normal appearance, and the paræsthesiæ had diminished. Hæmoglobin 88 % (13.0 g), erythrocytes 4,180,000, colour index 1.00. A bone-marrow examination showed that the perniciosiform maturation disturbances in the granulopoiesis had almost disappeared.

Case 8. A man (D. N. 2723), aged 52, complained of paræsthesiæ and dysæsthesiæ of feet and legs of three years' duration and of progressive unsteadiness of gait. For one month he had had paræsthesiæ of the left palm and difficulty in guiding both upper extremities.

Physical examination. There were a slight reduction in the muscular power of both hands and loss of finer co-ordination of the fingers. The abdominal reflexes were absent. Decreased tone of the lower extremities with weak knee jerks, absent ankle jerks, abolished sense of position and pronounced ataxia was observed. The plantar reflexes were normal. There were hypæsthesia and hypalgesia of feet and legs. The gait was ataxic, and the patient was unable to walk unsupported.

Laboratory findings. The spinal fluid showed 0 cells per cu.mm, normal protein content (Bisgaard 11), and a negative Pandy reaction. The Wassermann reaction in blood and spinal fluid was negative. Histamine-fast achlorhydria was demonstrated.

Blood examination showed hæmoglobin 83 % (12.2 g), erythrocytes 3,240,000, colour index 1.22, leucocytes 7,600, normal smear.

The bone marrow revealed an intense erythropoiesis with many large, immature precursors, mainly large, basophilic normoblasts but also a few intermediate megaloblasts. The granulopoiesis showed pronounced maturation disturbances in the form of giant metamyelocytes, giant stab cells and macropolycytes. The megakaryocytes were normal.

Treatment and course. The patient was given a desiccated hog's stomach preparation (Exo-Pylorin MCO, 10 g daily) and intramuscular injections of Hepsol Fortior, 5 ml every fifth day. Three weeks later the patient had only slight subjective discomforts. The gait had improved so much that he was able to walk freely and almost without staggering. There were still abolished sense of position, weak knee jerks, absent ankle jerks and hypæsthesia and hypalgesia of the legs, but the manual clumsiness and the decreased tone and ataxia of the lower extremities had disappeared. The hæmoglobin level had increased to 94 % (13.9 g), and the erythrocyte count to 4,370,000, colour index 1.03.

Five years later we were informed by letter that the patient was completely free of subjective discomfort, and that he had constantly received anti-pernicious-anæmia treatment.

Comments.

It is a generally accepted view that despite the presence of only slight hæmatological changes pernicious anæmia may be accompanied by severe glossitis and/or neuropathy. As, however, such cases are difficult of interpretation, the reliability of the diagnoses made in the present series will be discussed below.

In all eight cases the clinical signs were suggestive of pernicious anæmia. Seven of the patients had chronic glossitis; six of these had also subacute combined degeneration of the cord, and one had combined degeneration without glossitis. In several of the patients a diagnosis of pernicious anæmia had previously been con-

sidered but had nevertheless been excluded because of the presence of normal hæmoglobin values. The problems which are discussed below are whether glossitis and neuropathy may be taken as expressions of a latent pernicious anæmia in spite of normal hæmoglobin levels, and if this be so, what evidence can be adduced in support of a diagnosis of deficiency of the anti-pernicious-anæmia factor.

Lingual symptoms. In the seven cases with chronic glossitis, the symptoms had persisted for comparatively long periods; in one patient for about six months, in the others from 12 months to 15 years. The soreness of the tongue had varied in intensity, and in all cases the condition had at intervals been very troublesome. Several of the patients had for long periods been treated by laryngologists without relief.

On admission, all seven patients complained of pain and burning in the tongue. In five of them, physical examination revealed a fiercely red and smooth tongue. In one case, the tongue was deeply fissured and coated, but without redness or papillary atrophy, and in another the lingual mucosa appeared perfectly normal in spite of pronounced burning of the tongue.

The lingual signs and symptoms improved after treatment for from 5 to 14 days. In five cases the symptoms disappeared completely, while some improvement was obtained in two. In four of the cases the patients were kept under observation for at least six months, and in these the improvement of the lingual symptoms was maintained by the continued therapy.

The clinical response to the specific anti-pernicious-anæmia therapy is strongly in favour of the assumption that the glossitis was due to deficiency of the anti-pernicious-anæmia factor.

Liver therapy was used in five cases and, in two of them, supplemented with desiccated hog's stomach preparations. In two patients the lingual symptoms disappeared, and in a third some improvement was observed. That the symptoms did not disappear completely in the last of these cases does not weaken the assumption of their pathogenesis, since the glossitis of frank pernicious anæmia may be highly refractory to treatment. Cases are on record in which the glossitis of pernicious anæmia did not disappear until after additional treatment with pantothenic acid, riboflavin, or folic acid (Brown). It is not clear whether such cases are due to an additional deficiency which has developed on account of the specific anti-pernicious-anæmia treatment, or whether a disturbance in the absorption of substances other than the anti-pernicious-anæmia factor may also sometimes be present in pernicious anæmia. In some cases of frank pernicious anæmia the lingual symptoms may not disappear until liver has been given in doses which are several times larger than those necessary to obtain a satisfactory hæmatological response. In case 4 of the present series the lingual symptoms did not disappear until a very intensive anti-pernicious-anæmia treatment had been given. In comparatively rare cases, the deficiency of the anti-pernicious-anæmia factor may, perhaps, lead to irreparable changes in the tongue, just as is sometimes seen with the neurological complications. It might be conceived that the symptoms from the tongue encountered in such cases are of neurogenic origin.

In three of the cases reported here the symptoms disappeared completely during

parenteral treatment with pure *vitamin B₁₂*, and in one case the improvement was maintained by oral therapy with vitamin *B₁₂* + intrinsic factor (Bendogen GEA).

From several cases of frank pernicious anæmia it is well established that the glossitis caused by deficiency of the anti-pernicious-anæmia factor may be due to lack of vitamin *B₁₂*. Schieve and Rundles have described a case similar to those reported herein, with a normal hæmoglobin level but with an increased colour index; «the bone marrow showed early megaloblastic development». Spies et al. and Youmans have reported cases of non-anæmic nutritional glossitis responding to vitamin *B₁₂*, but bone-marrow examinations were not mentioned in these cases.

Neurological symptoms. In seven of the patients of the present series there were neurological symptoms similar to those encountered in pernicious anæmia. In all cases there were typical sensory disturbances in the form of paræsthesiæ and dysæsthesiæ. Symptoms from the posterior columns were present in six cases, evidenced by manual clumsiness or more pronounced ataxia of the upper extremities, or by ataxia of the lower extremities and, sometimes, by disturbances in the gait. In two of the cases there were also signs of pyramidal tract involvement in the form of Babinski's toe phenomenon and spasticity.

The symptoms had persisted for from 12 months to 15 years before the diagnosis was made, and before specific anti-pernicious-anæmia treatment was instituted. At that time the disease had led to complete disability in three of these cases, and in another two the patients were seriously troubled by the disturbed gait.

Attempts were made to rule out other neurological lesions which might produce the same clinical picture, such as cerebrospinal syphilis, arteriosclerosis of the spinal cord, multiple sclerosis, and polyneuritis. Spinal-fluid examinations performed in five of the cases did not reveal any abnormalities.

In association with specific anti-pernicious-anæmia treatment definite improvement occurred in four of the cases. In case 6 suffering from moderate neurological disturbances in the form of manual clumsiness and paræsthesiæ the signs and symptoms subsided after parenteral administration of vitamin *B₁₂*, and 12 months later the improvement had been maintained by oral therapy with vitamin *B₁₂* + intrinsic factor (Bendogen GEA). In case 8 there were severe neurological disturbances with pronounced instability of gait. The symptoms disappeared completely during treatment with desiccated hog's stomach and liver extracts, and the symptoms did not return during an observation period of five years, during which time the patient received first the above-mentioned drugs and later injections of vitamin *B₁₂*. In cases 4 and 7 the paræsthesiæ diminished during the liver therapy.

The anti-pernicious-anæmia treatment did not result in any definite improvement of the neurological symptoms in the remaining three cases, but, at least, the symptoms did not progress during the maintenance therapy.

The improvement obtained in the aforementioned four cases must be attributed to the anti-pernicious-anæmia treatment, and is thus in favour of the assumption that the neurological symptoms were due to deficiency of the anti-pernicious-anæmia factor. No significance can be attached to the fact that no improvement was obtained in the remaining three cases, since degenerative changes of the central nervous system occurring in pernicious anæmia are considered to be irrepara-

Table 1.

The peripheral blood

in 8 cases of glossitis and neuropathy with normal hæmoglobin levels and histamine-fast achlorhydria. The response to anti-pernicious-anæmia therapy.

Case	Before treatment			After treatment		
	Hæmoglobin	R. B. C.	Colour index	Hæmoglobin	R. B. C.	Colour index
	% (g)			% (g)		
1.....	85 (12.6)	3.58	1.13	92 (13.6)	4.88	0.96
2.....	87 (12.9)	3.80	1.10	87 (12.9)	4.23	1.00
3.....	89 (13.2)	3.48	1.22	87 (12.9)	4.47	0.98
4.....	92 (13.6)	3.30	1.33	90 (13.3)	4.02	1.07
5.....	90 (13.3)	3.80	1.12	90 (13.3)	4.20	1.02
6.....	100 (14.8)	3.57	1.33	100 (14.8)	4.50	1.11
7.....	90 (13.3)	3.14	1.36	88 (13.0)	4.18	1.00
8.....	83 (12.2)	3.24	1.22	94 (13.9)	4.37	1.03

table if the symptoms have persisted for more than six months. The fact that specific treatment seems to have prevented further progression of the disease in these three cases, which were observed for 1—2 years, is in favour of the view that there was a deficiency of the anti-pernicious-anæmia factor.

Blood examinations. The results of the examinations of the peripheral blood before and after the institution of anti-pernicious-anæmia treatment are shown in table 1. The hæmoglobin values were within normal limits, ranging from 83 to 100 % (12.3—14.8 g). An increase in the hæmoglobin values after anti-pernicious-anæmia treatment was seen only in two cases, whereas the level remained unchanged in the remaining six cases, even though the erythrocyte counts increased. In these six cases it must therefore be taken for granted that the measured hæmoglobin values actually represented the normal levels for the patients in question.

Prior to the institution of the anti-pernicious-anæmia treatment all the patients showed diminished erythrocyte counts (3.14—3.8 million), resulting in increased colour indices. After the treatment all the patients showed a definite increase in the erythrocyte counts, and the colour indices returned to normal.

The colour index was only moderately increased. In four cases it exceeded 1.20; in three cases it was but slightly above 1.0 (1.10—1.13), so that it could not be decided with certainty whether or not the increase was significant. Accordingly, decisive importance was not attached to this finding; it was used only in support of other observations which might suggest a deficiency of the anti-pernicious-anæmia factor, for example, increases in the erythrocyte counts during the specific treatment. The significance of this response to treatment cannot be questioned.

The leucocyte counts were normal.

The results from the bone-marrow examinations appear from table 2 and figures 1—4. In six of the cases the erythropoiesis was perfectly normal, whereas two cases showed slight changes in the form of intermediate megaloblasts. However, as an isolated phenomenon this observation is of no value. None of the cases showed

Table 2.

The bone marrow

in 8 cases of glossitis and neuropathy with normal hæmoglobin levels; and the response to anti-pernicious-anæmia therapy.

Case	Before treatment		After treatment	
	Granulopoiesis (pernicious-anæmia neutrophils. Per cent of total neutrophils)	Erythropoiesis (i. m. = intermediate megaloblasts. Per cent of total nucleated red blood cells)	Granulopoiesis	Erythropoiesis
1.....	8 %	normal	normal	normal
2.....	7 %	normal	normal	normal
3.....	15 %	2 % i. m.	normal	normal
4.....	10 %	1 % i. m.	normal	normal
5.....	12 %	normal	normal	normal
6.....	4 %	normal	normal	normal
7.....	6 %	normal	normal	normal
8.....	12 %	normal	—	—

any abnormalities in the *thrombopoiesis*. The megakaryocytes were morphologically normal, and so was the platelet formation.

In all the cases, the presence of «pernicious-anæmia neutrophils» was a very characteristic feature in the bone-marrow examinations. These cells were giant metamyelocytes and giant stab cells in which the nucleus had an immature appearance with a rather loose chromatic structure, while it had the indented form of the metamyelocyte (figs. 1—2) or the stab cell (figs. 3—5), i. e., there was a dissociation of maturation in nuclear structure and shape. The giant stab cells were often of bizarre shapes, the nuclei being lobulated or distorted (fig. 5). Furthermore, some hypersegmented neutrophils (macropolycytes) were present (fig. 6). Morphologically, all these cells corresponded to the changes which are observed in the granulopoiesis in frank pernicious anæmia.

In six of the cases the bone marrow was examined after two to four weeks' anti-pernicious-anæmia treatment. In these cases the previously observed maturation disturbances had disappeared at the time of examination.

Thus, the hæmatological findings which in this series provided evidence suggesting a deficiency of the anti-pernicious-anæmia factor were: diminished erythrocyte counts, increased colour indices (despite normal hæmoglobin values), and, particularly, the occurrence of «pernicious-anæmia neutrophils» in the bone marrow (despite normocytic erythropoiesis). However, conclusive proof of this diagnosis was provided by the response to specific anti-pernicious-anæmia treatment, since this treatment resulted in an increase in the erythrocyte counts and in a return to normal of the bone marrow.

It is reasonable to assume the existence of a relationship between the clinical symptoms and the deficiency of the anti-pernicious-anæmia factor. The fact that the lingual symptoms responded to specific treatment in all cases and the neurological symptoms in four is in favour of this assumption.

Symptomatic deficiency of the anti-pernicious-anæmia factor as may be seen

in nutritional deficiency states, in disorders of the digestive tract and in liver disease could be excluded. Coupled with the long duration of the symptoms and the presence of achlorhydria, this was strongly in favour of a diagnosis of essential pernicious anaemia. A clinical picture like the one described here, with glossitis and neuropathy but with only slight haematological changes, may be encountered in patients with pernicious anaemia who have received inadequate treatment. However, none of the patients from this series had received any preparations with anti-pernicious-anaemia activity prior to admission. It is therefore reasonable to assume that they were suffering from pernicious anaemia with a normal haemoglobin level. Owing to the lowered erythrocyte values it is justifiable to speak of *anæmia* in these cases, since anaemia must be defined as a state in which there is a reduction in the amount of haemoglobin or in the number of erythrocytes, or in both.

Conclusions.

In the cases reported herein the presence of glossitis and/or myelopathy might arouse suspicion of pernicious anaemia. However, a result of the normal haemoglobin values observed in most of these cases seems to have been that the patients were examined with special reference to this disease only at a late stage of its development.

This study shows that even though a patient may have haemoglobin values within the normal range or even at the level which is normal for the patient in question, pernicious *anæmia* with a depression of the erythrocyte counts may very well be present.

Deficiency of the anti-pernicious-anaemia factor may cause both megalocytic anaemia, glossitis, and subacute combined degeneration of the spinal cord. It is generally accepted that there need not be any correlation between the degrees of the glossitis, the neuropathy, and the anaemia, which is also confirmed by the observations in the present series. Moreover, this case material shows that both glossitis and myelopathy may persist for long periods and be far advanced, although the disorder of the blood is so inconspicuous that it may easily pass unnoticed. Consequently, the presence of a normal haemoglobin level does not obviate an extensive blood examination, if the patient exhibits signs of deficiency of the anti-pernicious-anaemia factor.

In spite of a normal haemoglobin level the presence of an increased colour index (and volume index) may point in the direction of a diagnosis of pernicious anaemia, but the most unequivocal signs of a deficiency of the anti-pernicious-anaemia factor are disclosed by the examination of the bone marrow. At the high erythrocyte counts found in such cases only very slight maturation disturbances in the precursors of the red cells or none at all can be expected, but in spite of this the granulopoiesis may reveal fairly distinct signs of deficiency of the anti-pernicious-anaemia factor in the form of «pernicious-anaemia neutrophils» (giant myelocytes, giant stab cells, and macropolocytes).

Glossitis of long standing, or signs of combined cord disease associated with histamine-fast achlorhydria, should arouse suspicion of a latent pernicious anaemia.

The presence of hyperchromic anæmia (even with a normal hæmoglobin level) and of »pernicious-anæmia neutrophils» in the bone marrow is in support of this diagnosis. However, it should be pointed out that in such cases (just as in frank pernicious anæmia) it is very important to follow the response to anti-pernicious-anæmia treatment. The fact that the hæmatological response is obviously not so dramatic as in pronounced pernicious anæmia should not induce one to omit close observation of the response in such patients. When the erythrocyte counts are so high as those observed in the present series, an increase in the number of the reticulocytes cannot be expected. On the other hand, the therapy must result in an increase of the number of erythrocytes, if low counts are obtained prior to the institution of the course. In addition, it is important to compare the bone-marrow findings from before and 2—3 weeks after the institution of the treatment in order to examine whether cells which have been interpreted as »pernicious-anæmia neutrophils» have disappeared. In this connexion it should be remembered that in treatment of pernicious anæmia the granulopoiesis returns to normal at a considerably later stage than the erythropoiesis. While a megaloblastic erythropoiesis becomes normoblastic in the course of 1—2 days, it often takes 1—3 weeks before the granulopoiesis returns to normal.

Obviously, the improvement of the sore tongue and of the neurological symptoms provides essential evidence in support of the correctness of the diagnosis. Although a glossitis due to deficiency of the anti-pernicious-anæmia factor may occasionally be relatively refractory to treatment, it will in most cases be cured within 1—2 weeks. The neuropathy may regress if it has not persisted for too long a period, and if it is treated with anti-pernicious-anæmia factor in doses 2—4 times as large as those required for the cure of the hæmatological disorder, but one should be prepared for the contingency that a deficiency having persisted for more than six months may leave behind irreparable changes, so that the absence of improvement does not necessarily speak against the correctness of the diagnosis. Also in such cases the anti-pernicious-anæmia treatment should be continued in order to prevent further progression of the disease.

If, in a case of glossitis, specific treatment is discontinued after the lapse of some time, because it is doubted that the case in question is one of true pernicious anæmia requiring continuous treatment, it is necessary that the patient be closely followed after the discontinuance in order to ensure that neurological symptoms do not develop. If there are concurrent neurological symptoms, the probability of the presence of pernicious anæmia is so great that, in view of the risk of progression of the neuropathy, it must be considered to be inadvisable to discontinue the treatment.

Summary.

Seven cases of chronic glossitis, including six with concurrent signs of more or less severe subacute combined degeneration of the spinal cord, are reported. The report also includes a case in which neurological manifestations, unassociated with glossitis, were present. These manifestations were suggestive of pernicious anæmia.

In several of the patients, this diagnosis had previously been considered, but yet had been excluded due to the presence of normal haemoglobin values.

Nevertheless, the results of closer haematological studies suggested that, in spite of normal haemoglobin levels, the patients were suffering from deficiency of the anti-pernicious-anæmia factor, evidenced by a slight diminution of the erythrocyte counts and increased colour indices. The most significant finding was, however, the presence of «pernicious-anæmia neutrophils» (*i. e.* giant metamyelocytes, giant stab cells and macropolycytes) in the bone marrow in spite of a normal erythropoiesis.

In association with anti-pernicious-anæmia treatment (liver extract or vitamin B₁₂) the erythrocyte counts increased and the colour indices returned to normal. The «pernicious-anæmia neutrophils» disappeared from the bone marrow. The lingual symptoms disappeared or improved, and in four cases improvement of the neurological symptoms also occurred. It seems reasonable to assume that both the glossitis and the neurological manifestations were due to deficiency of the anti-pernicious-anæmia factor.

Symptomatic deficiency of the anti-pernicious-anæmia factor as may be encountered in nutritional deficiency states, in various disorders of the digestive tract and sometimes in liver disease could be excluded. Coupled with the long duration of the symptoms (6 months to 15 years) and the presence of achlorhydria, this was strongly in favour of a diagnosis of essential pernicious anæmia.

The type of pernicious anæmia described, with a normal haemoglobin level, may lead to serious discomforts to the patient (severe glossitis and incapacitating myelopathy) if it is left untreated. It is therefore emphasized that bone-marrow examinations may be of diagnostic value in such cases, provided that it is borne in mind that perniciosiform maturation disturbances may occur as an isolated phenomenon in the granulopoiesis.

References.

- Brown, A.: *British Medical Journ.* *i*, 704–706, 1949. — Doig, R. K., Motteram, R., Robertson, E. G. & Wood, I. J.: *The Lancet* 259, 836–841, 1950. — Schieve, J. F. & Rundles, R. W.: *Journ. of Lab. and Clin. Med.* *31*, 439–447, 1949. — Spies, T. D., Lopez, G. G., Milanes, F., Stone, R. E., Toca, R. L., Aramburn, T. & Kartus, S.: *Blood* *4*, 819–826, 1949. — Whitby, L. E. H. & Britton, C. J.: *Disorders of the Blood*. Churchill. London 1950. — Wintrobe, M.: *Clinical Hematology*. Lea & Febiger. Philadelphia 1951. — Youmans, J. B.: *Transact. of the Ass. of Am. Physicians* *61*, 304–309, 1951.
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Deep Venous Thrombosis in the Lower Limbs as a Complication of Internal Diseases.

By

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Prophylaxis is naturally considered particularly important in postoperative and postpartum thrombo-embolism. The period of rest in bed is shortened as far as possible, and exercises for the legs and feet are recommended. Furthermore anticoagulants have been used with good results by many clinicians.

When thrombo-embolism occurs as a complication of internal diseases the situation is different. Preventive treatment cannot play a major part for the reason that the patients are not always under the care of a physician when they are in the »danger zone». Furthermore their condition very often does not allow of any exercises, and the basic complaint may even in some cases constitute a contraindication to prophylactic measures of any kind. It is, however, important that the clinician knows which diseases are prone to be complicated by thrombosis and therefore »lifts the blanket» now and then with this possibility in view. It should also be borne in mind that pulmonary infarction may occur without any characteristic symptoms of thrombosis from the legs. The situation seems to be that many cases are not diagnosed correctly, the pulmonary symptoms being instead attributed to pneumonia.

Since effective treatment became possible in the nineteen thirties, the importance of an early and certain diagnosis has increased. Today a combination of heparin and dicumarol or some related preparation is mostly used. The purpose of this therapy is to obtain rapid relief with heparin; later, when dicumarol has taken full effect, this is given alone. Treatment is thus commenced by simultaneous administration of both preparations.

It is difficult to use the anticoagulants judiciously owing to individual variations in the appropriate dosage and to the difficulties involved in checking the effect of

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the drugs in each case. This statement applies in particular to dicumarol and to the determination of its effect on blood coagulation, which was previously always performed by the method of Quick or some modified version. Since 1951 Owren's method has come into use particularly in the Northern countries. According to our experience it is the best for clinical use.

The time a patient is kept in bed, the frequency of complications, the death rate in pulmonary embolism, and the frequency and degree of post-thrombotic sequelae are considered as criteria for the efficiency of the treatment. Extension of the thrombus, formation of another thrombus, and pulmonary infarction must be regarded as complications. The reliability of the principles on which the dosage is based may be judged by the incidence of haemorrhages during treatment, provided that no factors constituting a contraindication to anticoagulant therapy have been overlooked.

Extensive surveys of postoperative and postpartum thrombo-embolism are available in the literature. The reports on thrombo-embolism in conjunction with internal diseases are much fewer.

In order to analyse this relation the records on thrombosis from the Medical Departments of the Maria Hospital — the IVth Medical Clinic and the Municipal Medical Department (Head: Guido Tötterman, M. D.) — from the period 1936—1952 have been studied. The total number of patients treated for the form of thrombo-embolism here concerned was 435, of which 328 (75.5 per cent) were females and 107 (24.6 per cent) males. The distribution according to age and sex is shown in Table 1. Middle-aged and elderly women are apparently most prone to be affected by this disease.

Table 1.
*Distribution of the total material according
to age and sex (1936—1952).*

Age	No. of patients	
10—19	2	
20—29	18	
30—39	42	
40—49	89	328 males
50—59	103	107 females
60—69	124	
70—79	54	
80—89	11	
Total number	435	

If the cases of thrombosis are calculated as a percentage of the total annual number of hospitalized patients, a marked, continuous increase is discernible from 1948 onwards (Fig. 1). This is probably due to the fact that the necessity of admitting these patients to hospital is now more generally accepted than before, rather than to a real increase in the incidence.

The journals from 1950—1952 have been analysed especially with a view to

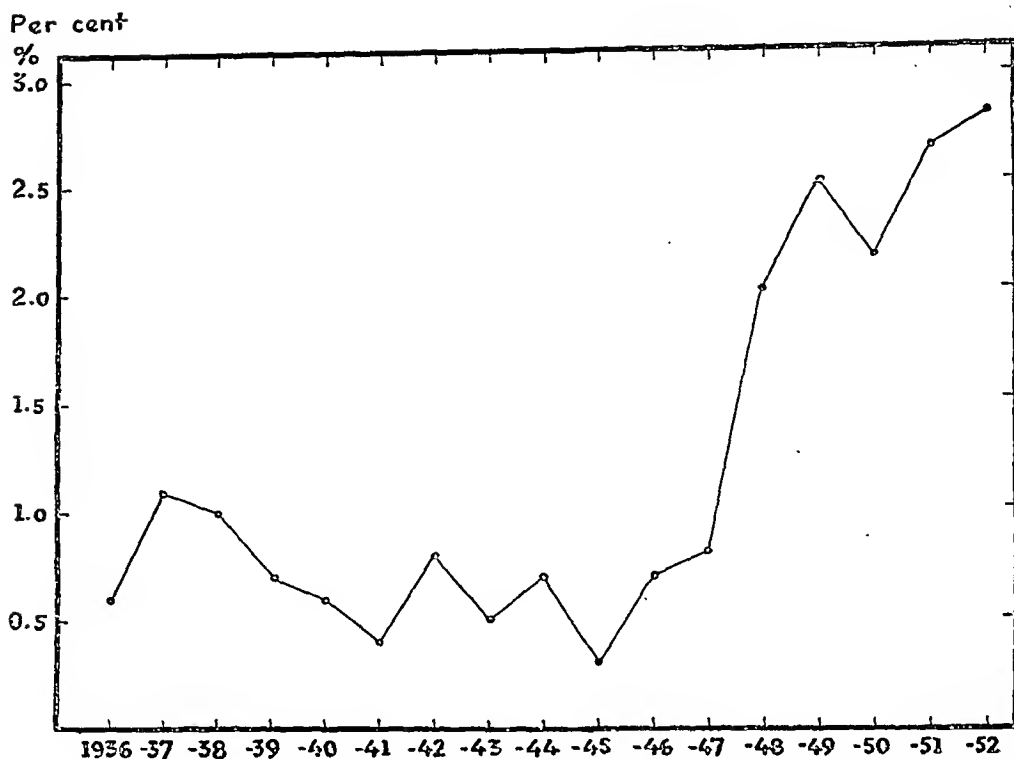


Fig. 1. Cases of thrombosis as a percentage of the total number of patients hospitalized at the Medical Departments of the Maria Hospital during the period 1936—1952.

ascertaining which diseases had been the basic reason for the development of a thrombo-embolic condition.

In 79 (44.3 per cent) of 178 cases obvious symptoms of *cardiac disease* with congestive failure were present. In these cases it is probable that venous stasis in the lower extremities was the chief precipitating factor. It cannot, however, be regarded as the only cause, since it would then be difficult to understand why congestive failure is not more often complicated by deep thrombosis in the lower extremities.

Diseases of the blood are sometimes accompanied by deep thrombosis. Polycythaemia vera is often complicated by this lesion. Previously thrombosis seems to have been a frequent occurrence in chlorosis, and myelogenous as well as lymphatic leukemia and pernicious anaemia in remission are conditions prone to be thus complicated. Of 24 (13.5 per cent) patients with haematological changes, 18 had normo- or hypochromic anaemia with a Sahli value under 60. In these cases it is not at all certain, however, that the anaemia was involved in the development of thrombosis. The other cases with changes of the blood were one cryptogenetic pernicious anaemia, 3 pernicious tapeworm anaemias and 2 myelogenous leukemias.

Most *infectious diseases* are sometimes complicated by deep thrombosis. The incidence has been given by Allen, Barker and Hines (1946) as 3 per cent in typhoid fever and as 0.6 per cent in pneumonia. In the present series infection may have

been involved in 26 cases (14.6 per cent). Infection in the respiratory organs represented the largest group, viz. 12 cases; 8 of these patients had pneumonia.

It seems natural that *malignant tumours* in an advanced stage should be complicated by thrombosis, but it is surprising and noteworthy that a thrombus in the lower limbs may be the first manifestation of a malignant process. It has been indicated that thrombosis occurs as an early complication principally in cases of carcinoma of the pancreas or lungs. In the present series, the total number of cases was 6 (3.3 per cent). The lesion developed at an early stage of the basic disease in one case only; in the remaining 5 it occurred as a late complication.

Trauma had obviously been the causative factor in 8 cases (4.5 per cent). In 11 (6.1 per cent), the formation of a thrombus may have been due to *pelvic conditions* such as pregnancy or extensive myoma. *Thrombangitis obliterans*, which undoubtedly is an illness predisposing to deep venous thrombosis in the lower extremities, had been diagnosed in 5 cases (2.8 per cent).

Varices of the leg may follow deep thrombosis, or occur primarily. According to Servelle (1948; cited by Højensgård), the enlargement of the veins has been preceded by deep venous lesions in 80 per cent of all cases considered as primary varicose disease. The rôle of varices as a predisposing factor in deep venous thrombosis is thus debatable. In the present series the incidence of this lesion is rather high, viz. 29 cases, or 16.2 per cent. If the large number (*i. e.* 56 cases, or 31.4 per cent) of patients treated for recurrent thrombosis is compared with the incidence of varicose disease, the deduction may perhaps be drawn that the occurrence of varices in the present series is to be considered as essentially a secondary phenomenon.

In 10 cases (5.6 per cent) *no obvious cause* for the development of thrombosis could be ascertained on the basis of the records. It is a noteworthy fact that obvious cases of deep thrombosis with a tendency to recurrence, the aetiology of which has remained obscure, have occurred from time to time in this hospital. The patients have as a rule been middle-aged men, and the frequency of such cases during short periods of time has caused some surprise. Two cases have been diagnosed as thrombophlebitis migrans.

From the standpoint of preventive treatment it is of some interest to know how many patients at rest in bed develop deep thrombosis during hospitalization. The rather high incidence — 41 cases (23 per cent) in the present series — shows that preventive measures are called for also in cases of internal disease. As a rule these, however, consist only in recommending the patient to exercise his legs and feet, and to perform respiratory exercises in the form of deep breathing, if possible.

It has been claimed that the drugs generally used in the treatment of cardiac insufficiency — digitalis and Hg-diuretics — increase the coagulability of the blood (Pere 1950). In view of the fact that the basic disease of the patients concerned predisposes to thrombosis it is difficult to say whether the formation of deep thrombi is influenced by the above-mentioned, alleged effect of these drugs. In the present series digitalis and/or Hg-diuretics had been given in 47 cases (26.4 per cent).

The relatively greater rate of deep thrombosis in the left lower extremity has

been adduced in support of the theory that venous stasis is an essential aetiological factor in this lesion. This argument is based on the fact that the vena cava caudalis is situated to the right in the pelvis; the blood in the left vena iliaca has therefore to flow a longer distance. Furthermore the left vena iliaca communis is crossed by the right arteria iliaca communis and the left arteria hypogastrica; it is possible that a resulting pressure on the vein may be a contributing cause of venous stasis. To ascertain whether any relation exists between these facts and deep thrombosis in patients with internal diseases, the journals from the period 1946—1952 were examined from this standpoint. The total number of cases was 314. The lesion was located to the left side in 157 cases (50 per cent) and to the right in 117 (37.2 per cent); in 40 cases (12.8 per cent) it was bilateral. These values speak in favour of an involvement of venous stasis.

Some investigators hold that the formation of a thrombus is in part dependent on the erythrocyte aggregation, which is contingent on the protein composition of the blood and influences the sedimentation reaction. The sedimentation rate would thus be a criterion of the disposition to thrombosis; in other words, a thrombus should not develop when the sedimentation rate is normal. It was found that as many as 23 patients (12.9 per cent) in the present series had an ESR value of less than 10 mm/hr at the time when they developed thrombosis. This seems to indicate that erythrocyte aggregation is not a major factor in the aetiology of the form of thrombo-embolism here concerned.

During the period 1936—1949, 257 patients with deep venous thrombosis in the lower limbs were admitted to the Medical Departments of the Maria Hospital. The records have been examined with a view to comparing the cases (133) subjected to anticoagulant therapy controlled by Quick's method and those (124) not so treated (Table 2). The rate of pulmonary embolism is about the same in the two groups, and the incidence of fatal embolism is also broadly similar. This fact is surprising and deserves of further analysis.

The above-mentioned figures include all cases of pulmonary embolism, viz. patients who displayed pulmonary symptoms already on admission as well as cases in which embolism occurred during hospitalization. In this connection the incidence during anticoagulant therapy is of significance. Of the total number of patients in this series 3 per cent were complicated by pulmonary embolism, and the outcome was fatal in 0.7 per cent. Considering that 25 per cent of the pulmonary complications and 14.2 per cent of the deaths occurred during anticoagulant therapy, the efficiency of the treatment seems rather doubtful. It is difficult to make a direct comparison with the cases not treated with anticoagulants, but the total number of complications and the death rate, which are broadly similar in both groups, are discouraging. It seems thus as if the treatment, though relieving the discomfort and shortening the illness, had not been capable of preventing dangerous and apprehended complications. Statistical reports on recent results with anticoagulant therapy have been surveyed by Bruzelius 1945, Merz 1949, Halse 1950, and Schmid 1951.

Theoretically it should be possible to prevent the development of embolism with the aid of the anticoagulants in cases with marked symptoms from the lower

Table 2.
Pulmonary embolism during treatment with and without anticoagulants.
 Prothrombin control with Quick's method 1936-1949.

		133 cases treated with anticoagulants		124 cases not treated with anticoagulants	
		No.	Per cent	No.	Per cent
Cases of recovery	As a complication during anticoagulant therapy	4	3.0		
	As a complication during a period when anticoagulants were not given	12	9.0		
	Total	16	12.0	17	13.7
Fatal cases	Deaths during anticoagulant therapy	1	0.7		
	Deaths during a period when anticoagulants were not given	6	4.5		
	Total	7	5.2	6	4.8
Total number of cases		23		23	

extremities. It is known that, when phlebitis is present with resulting symptoms from the legs, the thrombus is in part at least adherent to the wall. »It is almost certain that a thrombus which is more than three days old will not become detached and a thrombus that is more than a few hours old will rarely become detached.» (Allen, Barker and Hines 1946.) The thrombus then propagates upwards, and it is this portion that may become detached. Propagation, and hence embolism, is counteracted by the anticoagulants. It thus seems as if the above-mentioned unsatisfactory results were attributable to an insufficient anticoagulative action. It is therefore of some importance to ascertain which drugs were administered when the emboli became detached. Of the four cases with pulmonary complications three had been treated with dicumarol and one with heparin. In the latter the complication occurred so early that it is uncertain whether the therapy had taken full effect. In the case with a fatal outcome dicumarol had been given.

It is a well-known fact that dicumarol therapy with Quick's prothrombin index as indicator often gives the clinician an uncertain feeling because the prothrombin values often vary very much even from one day to another. For this reason it is difficult to keep the coagulability of the blood on a low and steady level, and it is therefore possible that the thrombus actually propagates during certain phases of the disease, with a greater risk of embolism ensuing.

At the Maria Hospital Owren's method has been used since 1951. It has been found advantageous, the values obtained being more even; therefore the dosage has varied less from day to day than before. For the sake of comparing cases treated during the period when Quick's prothrombin index was determined and those in

Table 3.
Pulmonary embolism during treatment with anticoagulants.
 1949—1952

		Dosage of dicumarol determined on basis of the			
		prothrombin percentage (Owren) 108 cases		prothrombin index (Quick) 122 cases	
		No.	Per cent	No.	Per cent
Cases of recovery	As a complication during anticoagulant therapy	0	0	7	5.7
	As a complication during a period when anticoagulants were not given	20	18.5	17	13.9
	Total	20	18.5	24	19.7
Fatal cases	Deaths during anticoagulant therapy	2	1.8	2	1.6
	Deaths during a period when anticoagulants were not given	1	0.9	5	4.0
	Total	3	2.7	7	5.6
Total number of cases		23		31	

which Owren's method has been used, the relevant records from the period 1949—1952 have been analysed (Table 3).

With regard to complicating pulmonary embolism during anticoagulant therapy the results in the prothrombin percentage (Owren) group are satisfactory, no such case having occurred. In the prothrombin index (Quick) group the corresponding figure was rather appalling: 5.7 per cent during treatment. Mortality during treatment was the same in both groups. It should, however, be borne in mind that one of the cases with a fatal outcome in the »Owren group» was in a poor condition from the beginning. There is thus a significant difference in favour of the »Owren group». The results of this analysis seem in any case to indicate that Owren's method is much superior.

The high incidence of complicating, and of fatal pulmonary embolism, in both groups together, viz. 44 (19.1 per cent) and 10 cases (4.4 per cent) respectively, seems to be a normal phenomenon when internal diseases are complicated by thrombosis. The corresponding figures given by Zilliacus (1946) were 39 (31.2 per cent) and 18 (14.4 per cent); the total number of cases from medical clinics was 125.

The frequency of a clinically demonstrable progression of the thrombotic lesion during anticoagulant therapy must be regarded as indicative of the efficiency of the treatment. Extension into the deep veins of the other leg is easily observable; hence diagnostic errors are ruled out. Two such cases occurred, one in the »Owren group», the other in the »Quick group». In the latter there was moreover one case

of cardiac infarction complicated by deep thrombosis in the leg during dicumarol therapy.

The time a patient has been kept in bed on account of thrombosis does not always appear from the records. Nor is the duration of the anticoagulant therapy a reliable measure of the duration of the illness, since the administration of dicumarol may have been continued because of some other disease. The duration of the illness can thus be estimated only in cases treated for thrombosis alone, where the time of hospitalization is a valid index. A mean value was obtainable on the basis of 92 cases out of 230; it was found to be 15.9 days.

The only serious complication that may occur during anticoagulant therapy is haemorrhage. One case of haematuria occurred in the »Quick group» and another following treatment with heparin alone. In the cases in which Owren's method was used there were no haemorrhages.

No follow-up examinations have been performed.

The good results obtained with Owren's method as indicator for the dosage, and the absence of haemorrhages, seem to suggest that prolonged treatment of outpatients with dicumarol may prove successful for the future. Such treatment has been tried already in Norway, and to some extent also at the Maria Hospital.

References.

- Allen, E., Barker, N. and Hines, E.: *Peripheral vascular diseases*, Saunders, Philadelphia & London 1946. — Bruzelius, S.: *Acta chir. scand.* 92: supp. 100: 1945. — Halse, Th.: *Heparin und Heparinoide Dicumarol*, S. Hirzel Verlag, Zürich 1950. — Højensgård, I. C.: *Kronisk venos insufficiens i underextremiteterne*, Arne Frost-Hansens Forlag, København 1951. — Kallner, S.: *Arch. Int. Med.* 81: 126: 1948. — Merz, W. R.: *Helvetica Medica Acta* 16: supp. 24: 1949. — Merz, W. R.: *Die Behandlung der Thrombose und Lungenembolie mit Antikoagulantien*, S. Karger, Basel & New York 1950. — Pere, Soini A. N.: *Acta med. scand.* 139: supp. 251: 1950. — Schmid, Josef: *Die Blutgerinnung in Theorie und Praxis*, Verlag Wilhelm Maudrich, Wien 1951. — Wright, I. S.: *The pathogenesis and treatment of thrombosis*, Grune & Stratton, New York 1952. — Zilliacus, H.: *Acta med. scand.* 124: supp. 171: 1946. — Zilliacus, H.: *Acta chir. scand.* 99: 407: 1950.

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Pre- and Post-Operative Renal Function in Coarctation of the Aorta and Its Relationship to the Genesis of Hypertension.

By

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The physiopathological interpretation of the haemodynamic pattern of coarctation of the aorta is not universally accepted. The differences concern particularly the interpretation of the genesis of hypertension, which is considered by some authors to be the direct consequence of the mechanical conditions produced by stenosis of the isthmus. Other authors, on the contrary, consider hypertension to be correlated with an increase of the peripheral resistance, therefore similar in this respect, to essential hypertension.

Recently, the former interpretation which repeats the classical opinion (1, 2), has been affirmed by Hull (3), Bing et al. (4) and, through experimental research, by Gupta & Wiggers (5); the latter interpretation has been accepted by numerous authors following the interpretation originally introduced by Steele & Cohn (6,7), after having made a direct determination of the pressure in the arteries below the point of stenosis, using Hamilton's manometer.

The hypothesis that an increase of peripheral resistance also plays a rôle in the mechanism of hypertension has been deduced from the following observations: 1) in the upper limbs; increase of the arterial pressure in all its values (systolic, diastolic and mean) is followed not by an increased flow, but by a normal (2, 8, 9) or a decreased one; 2) in some cases the differential pressure of the arteries above, the stenosis is rather low, similar to typical findings in essential hypertension (11); 3) in the lower limbs, the diastolic pressure is generally frankly increased, and the mean pressure is not lower, but equal to or higher than the normal mean pressure (4, 7, 12—16); 4) the cardiac output is not decreased but normal and, sometimes, increased (17, 18); 5) both in upper and in lower limbs the arteriolar system preserves its ability to react to thermal stimuli and to some drugs (epinephrine, amyl-nitrite) and after the vasodilatation, the pressure values decrease and the blood flow increases (10, 12).

Moreover, considering a rarer condition, analogous to stenosis of the isthmus, namely the congenital coarctation of the abdominal aorta above the renal arteries (described already by Steele (7), and more recently by other observers (19-22), one must stress the fact, that sometimes not a constant hypertension, but a paroxysmal one, which might simulate a phaeochromocytoma has been observed (21). This observation corroborates, too, the hypothesis of the intervention of purely functional factors in the genesis of hypertension.

Even more favourable to such a hypothesis are the results of some recent experimental investigations. For example, in the dog, coarctation of the aorta through insertion of a leucite tube into the classical Botallian seat in such a way as to reproduce the characteristic conditions of the human malformation (23), is followed by an increase in the carotid pressure. This pressure does not become stable in a short time (as it would if it depended only on mechanical factors), but rises progressively over a period of several months, while in the femoral artery the diastolic and mean pressures decrease only in the period immediately following the production of the stenosis, increasing afterwards progressively till they almost reach the values found in the carotid artery (24, 25). Having proved in such a way the importance of the increase of the arteriolar tone and peripheral resistances in the genesis of the hypertension found in the coarctation of aorta, Steele & Cohn (6, 7) have postulated that this increase of pressure would depend on renal ischemia, following the interpretation by Goldblatt. Such a hypothesis has started a double line of inquiry: on the one hand experimental research on animals, and on the other hand the study of the renal function in man, with particular attention to renal circulation. Moreover, interest in such research has been stimulated by the first surgical successes (26, 27), which have transferred the problem to the clinicians, at the same time raising the question as to whether this operation although removing the mechanical obstacle, can resolve a hypertensive condition, dependent at least in part on other pathogenic causes.

The experimental researches in animals have corroborated the hypothesis of the presence of a hypertensive factor dependent on renal conditions (28-32). In fact, Scott & Bahnson, having established a termino-lateral anastomosis between the left subclavian artery and the thoracic aorta and divided the aorta above the obstacle, have succeeded for the first time in creating a condition which for the localization of the obstacle and for its haemodynamic results (increase of all the pressure values of the carotid artery, increase of the mean pressure in the femoral artery) is strictly comparable to that of human coarctation. In animals undergoing operation in this way, the transplantation of a kidney to the neck, followed by the removal of the contralateral kidney, causes the carotid pressure to go back quickly to the normal values.

The study of the renal haemodynamics, on the contrary, has not given completely unequivocal results. The first authors to undertake such research were Friedman et al. (34). They reported in 6 patients with coarctation of aorta that the renal plasma flow was substantially reduced and that the glomerular filtration rate was almost normal, giving rise to a markedly elevated filtration fraction. These results, identical with those characteristic of essential hypertension (36) (no investigations

were made into the tubular mass, however), are, according to the authors, significant of a real condition of renal ischaemia with hypertonus of the efferent arterioles.

Genest et al. (37), through the study of 17 cases, have reached somewhat analogous conclusions, though with certain discrepancies. These authors carried out their research by collecting the postoperative data also, in 12 of these patients. They have demonstrated that the improvement in the haemodynamic condition is paralleled by the improvement in the renal circulation. The postoperative modifications were as follows: the filtration rate increased in 5 patients, decreased in 2, was unchanged in 5; the renal blood flow increased in 7 patients, decreased in 2, remained unchanged in 4; the filtration fraction fell in 6 patients, increased in 4, remained unchanged in 2. Therefore, considered as a whole, the authors' data show that postoperatively the renal function becomes or approaches normal and this modification of the preoperative condition is paralleled by the improvement of the circulatory pattern.

Opposed to the data proving that renal ischaemia is an aetiological cause in coarctation of the aorta and favourable to the hypothesis that a humoral renal substance participates in the genesis of hypertension, are the observations collected by Harris et al. (16) in their study of 4 pre- and post-operative cases. In this series also the pre-operative data show, like the preceding ones, a decreased renal blood and plasma flow, however the data differs as regards the filtration rate which was decreased and the filtration fraction which was normal or increased. Moreover, the early post-operative data in 3 cases (from 7 to 11 days after surgical intervention varying in the different cases) showed a marked increase of the renal blood and plasma flow and of the filtration rate until the values were almost normal, accompanying the marked improvement on the circulatory side (at least concerning the brachial pressure). On the contrary the controls after a longer period (from 60 to 112 days) showed a return of the renal circulatory conditions to the pre-operative level, while the brachial pressure decreased further. Finally the fourth case gave a paradoxical result, because though the operation had no effect on the blood pressure, there was a marked improvement of renal circulatory conditions. To explain such discrepancies the authors suppose that the first results of the renal clearances in such a case were colored by emotional factors, which are known to effect such tests markedly (39). According to the above results, Harris et al. deny the existence in aortic coarctation of a relationship between the arterial pressure and renal circulatory conditions. Though they recognize that the characteristic haemodynamic alterations cannot be explained completely on the basis of mechanical factors, they exclude renal ischaemia as the pathogenic factor of hypertension. However, from a critical point of view, we must report that post-operatively, the systolic and mean pressures in the femoral artery were increased in 1 case, unchanged in 1 case and decreased in 1 case; the pulse pressure increased in 2 cases and decreased in 1. These post-operative data, in fact, differ among themselves and are at variance also with those of preceding authors (1). Sufficiently so, in fact, to make us ask how far and in what sense had the circulatory condition below the stenosis been modified.

The same renal findings were obtained by Barker & Clark (39), who in 10 patients

verified that the renal plasma flow was at the low normal ranges and the filtration rate was practically normal. Post-operative control, carried out in 6 cases, showed a slight increase of the renal blood flow. In 2 cases studied for a longer post-operative time (2 years) a return to pre-operative conditions was demonstrated. In this short paper (summary of a paper given before the American College of Surgeons) there is no data concerning the pressure values and their relative post-operative modifications.

To conclude this bibliographical report, we wish to mention the experimental data by Sealy et al. (25), who have studied 4 dogs in whom a coarcting tube has been inserted for 3 to 4 months. These animals showed the characteristic pressure modifications and alterations of renal function, strictly comparable to those observed in the spontaneous pathology by Friedman et al. (34), namely a moderate decrease of the renal plasma flow, with progressive increase of the filtration fraction.

Thus, although (a) evidence from human coarctation indicates the deficiency of a mechanical theory and evidence from animals refutes it; (b) all investigators who recently have discussed the matter, agree that in the lower as in the upper extremities, both in humans and in animals, some other mechanism must contribute to the changes in vascular dynamics, which follow and may be initiated by the mechanical factors of obstruction; and (c) consequently some authors have supposed that the renal ischaemia may be responsible for these unexplained conditions, there is no agreement about the relationship between the genesis of hypertension in coarctation of the aorta and the kidneys and about the interpretation of the alteration of renal function, observed by all investigators in this disease. It has not therefore seemed to us unnecessary to report the results of research regarding renal function and dynamics, done in our Institutes, in 5 patients with coarctation of the aorta. All of these patients have been studied pre-operatively from the point of view of renal function. One has not had an operation. Three of the four operated have been studied after the operation; the fourth, a very apprehensive woman, would not co-operate after the operation.

Case Reports

Case I. B. Luigia, 26 years old.

Clinical History: The p. developed normally; she always lived a very active life, doing even hard manual work. When she was 17, she began to suffer with headaches, buzzing in the ears, dizziness and finally these troubles became more frequent and accentuated and the p. complained of precordial pains radiating along the left arm.

Physical Examination: A strong well nourished woman. Radial pulse full, distended, rhythmic, with a rate of 100–110/min. Femoral pulse hardly palpable. Accentuated carotid pulse. Cardiac area increased to the left; a systolic murmur at the apex, in the aortic valve area and in the left interscapulo-vertebral area. E.C.G.: left ventricular preponderance.

The thoracic roentgenogram shows marked hypertrophy of the left ventricle and presence of knuckles at the lower border of several ribs.

The aortography (performed through the external carotid artery) shows the presence of an isthmical stenosis of the aorta.

Surgical Intervention took place on June the 26th, 1952, by Prof. P. Valdoni. Left

posterolateral thoracotomy with subperiosteal resection of the 5th rib. The isthmical stenosis was about 4 cm long. The most narrow part corresponded to the arterial ligament. The stenotic tract was removed and continuity reestablished through a preserved aortic homograft,¹ 5 cm long applied through sutures with extroflexing separate U-points, redoubled by a continuous suture on the everse borders. Declivous drainage tube; suture of the wall.

Post-operative clinical course complicated by several anginoid crises. The p. was discharged recovered after 41 days.²

Case II. M. Dino, 28 years old.

Clinical History: Normal development; the p. did the hardest kind of work and also military training, fighting during the last war. During the preceding years he suffered moderate headaches; 6 months ago subarachnoid haemorrhage occurred, followed by coma, lasting 15 days.

Physical Examination: A strong man, with hypotrophy of the muscles of the lower limbs. The radial pulse was full, distended, rhythmic, with a rate of 95/min. An intense pulsation of the carotid, subclavian, axillary and intercostal arteries was seen. Visible arterial pulsations were seen on the back, in Campbell and Suzman's position (40); the femoral pulse being hardly palpable and appearing delayed, compared with the radial one. The cardiac area was increased to the left. E.C.G.: left ventricular preponderance.

Thoracic Roentgenogram: Presence of notches at the lower border of several ribs, bilaterally.

Surgical Intervention took place on May, the 2nd, 1952, by Prof. P. Valdoni. Left posterolateral thoracotomy, with subperiosteal resection of the 5th rib. Finding of an isthmical stenosis which began about 1 cm below the subclavian artery and became closed after about 1 cm; its total length being $3\frac{1}{2}$ cm. Resection of the stenotic tract was performed and rebuilding through a preserved aortic homograft, about 4 cm long, applied through the same technique as in the former case. Declivous draining tube; suture of the wound.

Post-operative clinical course uncomplicated; the p. was discharged recovered after 30 days.

Case III. L. Pier Luigi, 15 years old.

Clinical History: The p. developed normally; played sports. During the preceding year he suffered from headaches, moderate strain dyspnoea, tachycardia.

Physical Examination: A well developed young man. The radial pulse was full, distended, rhythmic, with a rate of 90/min. The femoral pulse was hardly perceptible. On the base of the neck the aortic arch could be palpated and showed full pulsations with a very intense systolic thrill. The carotid and axillary arteries pulsated also markedly; and at the back, the pulsation of the intercostal arteries could be palpated from the 5th to the 8th space, bilaterally. The cardiac area was increased to the left; an intense systolic murmur being heard in all the valvular areas and in the left interscapulovertebral area; a diastolic murmur in the aortic valve area and at the apex. E.C.G: left ventricular preponderance.

Thoracic Roentgenogram: Moderate increase of the cardiac area and particularly of the left ventricle; notches at the lower border of some ribs, bilaterally.

Surgical Intervention took place on Oct., the 18th, Prof. by P. Valdoni. Left posterolateral thoracotomy, with subperiosteal resection of the 4th rib. The coarctation was in the classical Botallian area, the stenotic tract being about 4 cm long. Resection of the stenotic tract and application of a preserved aortic homograft was performed with the same technique as in the former cases. Declivous drainage tube and suture of the wall.

¹ The homografts were preserved according to the method of Swan et al. (41).

² The pre- and post-operative pressure values and the results of the clearances of this case and of all the other ones are given in Table 1.

Post-operative clinical course uncomplicated; the p. was discharged recovered after 24 days.

Case IV. F. Alberto, 16 years old.

Clinical History: The p. developed normally. During the preceding years he suffered from headaches, cardiospasm and strain dyspnoea.

Physical Examination. A young man in good general condition. Radial pulse full, distended, rhythmic, with a rate of 68/min; femoral pulse hardly perceptible. The boundary of the cardiac area was normal; the heart sounds clear in all the valvular areas; a short systolic murmur in the left interscapulovertbral area. E.C.G.: left ventricular preponderance.

Surgical Intervention took place on June, the 28th, 1952, by Prof. P. Valdoni. Left posterolateral thoracotomy, with subperiosteal resection of the 4th rib. There was a blunt, eccentric stenosis, at the level of the arterial ligament. Resection of the stenotic tract and rebuilding of the continuity through a preserved aortic homograft, about 4 cm long was carried out, which was applied with the same technique as in the former cases. Declivous drainage tube; suture of the wound.

Post-operative clinical course uncomplicated; the p. was discharged recovered after 25 days.

Case V. P. Giuseppe, 16 years old.

Clinical History: Normal development. The p. was in good health until the age of 8 years, when, after a long race he suffered a sudden attack of cardiospasm and constricting pains in the retrosternal areas, lasting about 2 hours. Afterwards he suffered similar attacks, at first at intervals of 1 year, later every few months.

Physical Examination: A well-developed young man in good general condition. Radial pulse was full, distended, rhythmic, with a rate of 100/min; femoral pulse very small and delayed compared with the radial one; the carotid and axillary arteries at the aortic arch the base of the neck were pulsating markedly. Visible pulsations, on the back, bilaterally of some intercostal arteries, from the 5th to the 6th space. The apex beat was found at the 6th intercostal space in the midclavicular line; systolic murmur at the apex and, more intensely in the aortic valve area. E.C.G.: Left ventricular preponderance.

Thoracic Roentgenogram: A prominent and pulsating aortic arch; knobles along the lower borders of some ribs.

The p. has not yet had his operation, because at the present time we have no suitable graft.

Methods and Techniques.

As said, surgical intervention, which has been successful in all cases, consisted in the resection of the stenotic tract followed by rebuilding with preserved homograft (41, 42, 51, 52, 53). In at least 3 cases, there was an absolute indication for the use of homograft, for the stenosis was rather long; moreover, in 2 cases the patients' age (more than 25 years) made it possible that in the tract above the stenosis the aorta might be the seat of arteriosclerotic lesions. Finally, in our opinion, this method corresponds to all the requirements of an ideal rebuilding, both because the graft substitutes in an exact manner for the stenotic aortic tract which is resected and because, the mobilisation of the aorta being no longer necessary, it is possible to spare all the intercostal arteries or, at least, all the intercostal arteries which participate efficiently in the collateral circulation; in addition the longitudinal tension of the sutures is abolished. We are aware that the use of homografts

has been considered with reserve in relation to their biological evolution, however we think that both the experimental and clinical results permit us to formulate an opinion which may be considered favourable when the following conditions are observed, namely that the homografts used have been resected only a short time and that they have been carefully preserved.

The Glomerular Filtration Rate (*G. F. R.*) was determined by means of inulin clearance; the effective Renal Plasma Flow (*R. P. F.*) by means of Para-amino-hippurate clearance; the tubular excretory capacity (*Tm*) by means of Para-amino-hippurate (*Tm_{PAH}*). The first two clearances were done simultaneously. All the investigations were done in the morning with patients under basal conditions (having fasted for 12 hours) (55, 66, 35). Prior to the day of examination the nature of the tests and their purpose were discussed in detail so that the actual procedure would not cause apprehension which would interfere with renal dynamics. Preliminary to and during the test a large water intake was provided in order to maintain an adequate diuresis. After the primary injection, the plasma concentration was kept constant by means of a constant intravenous infusion, according to the technique of Smith (56). The plasma inulin level was maintained between 30 and 40 mgm %. The plasma PAH level was maintained between 1.5 and 3 mgm % for the clearance and between 40 and 60 mgm % for the *Tm*. Three periods of clearance were executed, the reported results being the mean of these three periods. All urines were collected through a multi-eyed catheter. The bladder was twice washed out at the end of each period with 50 cc of saline plus 50 cc of air.

Inulin was determined by the Harrison (57) modification of the Alving, Rubin and Miller method (58). PAH was determined by the method of Smith, Finkelstein, Alimiusa, Crawford and Graber (59).

All clearances were corrected to standard surface area (in man 1.73 sq. m.). The renal blood flow (*R. B. F.*) was calculated through the formula:

$$R. B. F. = C_{PAH} / (1 - \text{haematocrit}).$$

Secretory *Tm*, the maximum tubular secretory capacity for PAH, is a tubular function, which in most circumstances is taken as measuring the mass of functioning tubular tissue. It may be calculated through the formula:

$$Tm_{PAH} = U_{PAH} V - C_{In} P_{PAH} FW^1$$

Plasma clearances, *Tm_{PAH}* and arterial pressure (both brachial and femoral) recorded as *Pm* (mean of systolic and diastolic pressures) constituted the direct observations.

The derived data are the clearance ratios and calculated resistances. The ratios are: (a) inulin/PAH or filtration fraction (*FF*); (b) calculated renal blood flow per unit of functioning tubular tissue abbreviated as *RBF/Tm_{PAH}*; and (c) calculated glomerular filtration rate per unit of functioning tubular tissue, abbreviated as *GFR/Tm_{PAH}*.

The procedure suggested by Gomez (61) (see Smith, 55) is used in calculating apparent renal vascular resistances. The total renal resistance (*R*) is equal to the

¹ *FW* appears to have a value of 0.91 (Smith, 55).

sum of the segmental (series) resistances and, in conventional haemodynamic terms, may be calculated as the effective perfusion pressure divided by the blood flow, through this formula:

$$(1) \quad R = \frac{P_m - P_v}{Q} \cdot 1328 = R'_A + R'_E + R_v$$

where R = total renal resistances; R_A = afferent resistances; R'_E = net efferent resistances; R_v = venular resistances; P_m = mean arterial pressure; P_v = renal venous pressure; Q = R. B. F. in cc/sec.

The venular resistance (R_v) is equal to the decrement in pressure between the peritubular capillaries and the renal vein, divided by the renal blood flow, according to the formula:

$$(2) \quad R_v = \frac{H + h - P_v}{Q} \cdot 1328$$

where h = the mean oncotic pressure and H = the interstitial pressure.

The net efferent resistance (R'_E) is that presented by the parallel combination of the efferent arteriolar segment and the shunt through the glomerulus and peritubular capillaries, according to the formula:

$$(3) \quad R'_E = \frac{q}{\lambda Q} \cdot 1328$$

where: q = the filtration rate; λ = the gross permeability of the glomerular capillaries.

The afferent resistances (R_A), namely the resistance to the flow of blood in the afferent tract to the end of glomerular capillaries may be obtained by the formula (1) ($R = R_A + R'_E + R_v$), knowing all the other terms.

Results.

The Pre-Operative Study.

In all our cases, the pressure values were characteristic of coarctation of the aorta (Table I, IIa, IIIa) both in upper and in the lower extremities. The hypertension verified may be classified into the systolic-diastolic hypertensive group (the largest group in coarctation of aorta), the systolic and diastolic pressures being both above normal in the arm (62, 63, 64 65). Moreover, the diastolic pressure in the lower extremities was relatively increased in all the 4 cases in which it was measured, and also absolutely increased in 2 of them (the 4th and 5th case). Consequently, the differential or pulse pressure below the stenosis was much lowered.

Considering now the pre-operative results of renal function tests, we may divide them in 2 groups, according as R. P. F., R. B. F. and F. F. are within the ranges of normality or not.

The first one (first 3 cases) may be characterized therefore by the following conditions: normal value of the G. F. R.; deviation in the lower ranges of the effective R. P. F. and R. B. F.; normal F. F.

In the second group (last two cases) this tendency to the lowering of the effective R. P. F. and R. B. F. is accentuated so as to reach pathological values. The G. F. R. remaining normal, F. F. is remarkably increased. Because these changes

Table I.
Pre- and post-operative results in blood pressure, renal functions and resistances.

Case and time of observations	Blood Pressure		G. F. R., cc/min.	R. P. F., cc/min.	R. B. F., cc/min.	F. F.	R (dyn/s/cm ⁻²) × 10 ⁻³	R _A (dyn/s/cm ⁻²) × 10 ⁻³	R' (dyn/s/cm ⁻²) × 10 ⁻³	R _V (dyn/s/cm ⁻²) × 10 ⁻³	Tm mg/ min.
	Upper Limbs	Lower Limbs									
Case I											
Pre-operative	220/125		111	595	1,024	0.187					
After 2 days	160/95	120/?									
After 6 days	160/95	125/95									
After 20 days	140/90	145/90									
After 40 days	145/100	145/105									
Case II											
Pre-operative	195/90	110/75	119	651	1,085	0.183	5.986	2.256	1.80	1.93	
After 2 hours	180/100	160/100									
After 1 day	170/90	160/100									
After 5 days	170/100	160/80									
After 10 days	140/90	140/90									
After 20 days	140/70	140/80	135 + 14%	710 + 12 %	1,207 + 11 %	0.190 + 3%	5.742 - 4 %	2.272 0	1.82 0	1.65 - 14 %	
After 27 days	130/65	140/70									
Increment %											
Case III											
Pre-operative	190/110	80/75	122	581	976	0.209	5.810	1.525	2.045	2.24	
After 1 day	140/80	115/?									
After 10 days	160/95	120/80									
After 20 days	150/90										
After 24 days	140/70	120/80	118 - 3 %	659 + 11 %	1,143 + 17 %	0.179 - 17%	6.210 + 6 %	2.805 + 84 %	1.685 - 17 %	1.72 - 23 %	
Increment %											
Case IV											
Pre-operative	195/120	90/85	117	504	852	0.232	7.520	2.655	2.355	2.51	
After 2 days	160/100	120/?									
After 10 days	155/90	130/90									
After 20 days	150/80	140/90	125 + 6 %	608 + 20 %	1,135 + 35 %	0.206 - 11%	7.590 0	3.92 + 52 %	1.81 - 23 %	1.86 - 25 %	
Increment %											
Case V											
Pre-operative	190/95	105/85	122	400	727	0.305	9.350	3.27	2.78	3.30	86

Table II.

Mean pre-operative data (divided into 2 groups) in relation to the normal.

(a) Direct Observation.

Function		Normal	1st Group	2nd Group
G. F. R.	Mean	120	117	119
cc per 1.73 m ² .	Range		119-122	117-122
R. P. F.	Mean	688	609	452
cc per 1.73 m ² .	Range		581-651	400-595
R. B. F.	Mean	1,100	1,028	789
cc per 1.73 m ² .	Range		976-1,085	727-852
Tm _{PAH}	Mean	82	—	86
mg per 1.73 m ² .				
P _m mm Hg.	Mean	95	155	150
(upper limbs)	Range		142-172	142-157
P _m mm Hg.	Mean	100	85	91
(lower limbs)	Range		77-92	87-95
P _D mm Hg.	Mean	70	108	108
(upper limbs)	Range		90-125	95-129
P _D mm Hg.	Mean	73	75	85
(lower limbs)	Range		75	85

(b) Derived Values

Function		Normal	1st Group	2nd Group
F. F.	Mean	0.190	0.193	0.269
	Range		0.183-0.209	0.232-0.365
R	Mean	5.630	5.890	8.430
$\times 10^{-2}$	Increment		$\div 4\%$	$\div 48\%$
	Range		5.810-5.980	7.320-9.559
R _A	Mean	2.100	1.880	2.960
$\times 10^{-2}$	Increment		-10%	$\div 40\%$
	Range		1.525-2.256	2.655-3.270
R' _E	Mean	1.660	1.920	2.560
$\times 10^{-2}$	Increment		$\div 15\%$	$\div 54\%$
	Range		1.800-2.045	2.355-2.780
R _V	Mean	1.870	2.080	2.900
$\times 10^{-2}$	Increment		$\div 11\%$	$\div 54\%$
	Range		1.930-2.240	2.510-3.200

resembled those in the essential hypertension (36), we investigated the Tm_{PAH} in the 5th case with the most altered R. P. F. and F. F. and have found it to be normal. Consequently the derived ratios were as follows: GFR/Tm was normal and R. P. F. was decreased.

¹ only 1 case.

The same division into 2 groups appeared in the field of the apparent renal resistances calculated indirectly through Gomez' formulae (61). In the first group the total renal resistances R and the single ones R_A, R'_E and R_V , were within the normal range with a slight increase of R_V (Table II b). In the second group the total resistances were increased, this increase affecting more the venular and efferent segment, than the afferent one (Table I, Table II b).

The Post-Operative Changes.

After surgical intervention, the pressure values tended to become normal in all cases (Table I, Table III a). In particular brachial pressure tended to become lower and the femoral one to rise; moreover the pulse pressure below the stenosis tended to become normal. However some pressure abnormalities remained after operation. The mean and systolic pressures remained higher in the upper than in the lower extremities in all cases but one. The mean pressure was also higher in our patients than in normal subjects of the same age.

Table III.

Post-operative changes.

(a) Pressure changes (mean of all cases) in relation to the normal values.

	Upper Extremities		Lower Extremities	
	P_s	P_D	P_s	P_D
Pre-op. Mean	200	111	93	78
Post-op. Mean	142	77	136	88
Increment	- 29 %	- 30 %	+ 32 %	+ 11 %
Normal Mean	120	70	127	73

(b) Post-operative changes of renal data (less than ± 10 % = unchanged)

Function	Number of cases		
	Increased	Decreased	Unchanged
G. F. R.	1	0	2
R. B. F.	3	0	0
R. P. F.	3	0	0
F. F.	0	2	1
R	0	0	3
R_A	2	0	1
R'_E	0	2	1
R_V	0	3	0

The post-operative modifications of the renal function were uniform in the 3 cases studied (Table III b). In all cases an increase of the R. P. F. and R. B. F. was observed, but the amount of this increase was variable. The increase, for example, was slight in the cases in which the R. P. F. and R. B. F. had been in the normal ranges pre-operatively; in the case in which these functions had been excessively low, the increase was remarkable (Table I).

Considering the changes of the calculated values, we see that the F. F. became normal in the 3rd and 4th case in which it was increased. The total renal resistances were practically unchanged (Table III b) both in the cases in which they were normal, and in the case in which they were increased. There was however a change in segmental resistances, characterized by a decrease of the venular and efferent resistances and an increase of the afferent ones.

Discussion.

The pre-operative pressure data in our patients, namely a systolic-diastolic hypertension in the upper limbs and a very low pulse pressure in presence of normal or elevated diastolic pressures in the lower limbs, show that hypertension cannot result solely from the mechanical condition of aortic stenosis, but from a combination of this with another factor, probably a humoral or neurogenic one which increases the peripheral resistance and the diastolic pressure. According to many authors this increase could be produced by a relative renal ischaemia or a diminished pulse pressure in the kidneys through a situation analogous to the hypertension determined by the Goldblatt kidney. Therefore, leaving undiscussed the general problem of the renal genesis of essential hypertension in humans, which is criticized by many recent authors (Smith (55), pages 745—51; Melli (73)), we have studied whether there was a pathogenic relationship between our renal data (and those of the preceding authors, 16, 34, 37, 39) and the genesis of hypertension.

Before discussing the detailed results, we must stress that, although we have found some alterations in renal function, our data show that: (a) these renal changes were not constantly present in all patients, some cases being within the normal ranges, though the diastolic hypertension was constantly observed; (b) these changes were reversible with the correction of the mechanical condition. Therefore in consideration of the divergences in the pre-operative results in renal function, we have divided our patients into 2 groups.

The results in the first group agree with those of Harris et al. (16) and Barker & Clark (39). The tendency for R. B. F. to be low indicates a functionally small kidney, perhaps as a result of the long standing changes in blood pressure. This reduction is however very slight (in the lower ranges of normal) and the kidney may have a normal G. F. R., without a significant increase in the efferent resistances and consequently in the F. F. Such data and such an interpretation suggest that in these cases the changes in renal dynamics play no rôle in the alterations in blood pressure and represent a secondary side of the general haemodynamic pattern in coarctation of the aorta.

The findings in the second group agree with those of Friedman et al. (34), Genest et al. (37) and with the 4th case of Harris et al. (16) (we must stress however that these first two groups of authors have not measured the total excretory mass). The very low R. B. F. and the high F. F. show that the reduction of the blood flow is accompanied by an afferent arteriolar constriction. In fact the total renal resistances are increased, this increase being more accentuated in the venular and effer-

ent segments. Remembering that: (a) any increase in the efferent segment is accompanied by an increase in glomerular pressure and consequently in the F. F.; (b) that on the contrary, when the renal blood flow is reduced, by pure afferent constriction the filtration rate decreases; (c) and also that the increase in venular resistance increases the pressure in the peritubular capillaries and opposes the reabsorption of water, leading to an increase in the interstitial fluid (Smith 55); we may say that the renal pattern of these cases in the 2nd group is characterized by a reduction of the renal blood flow, accompanied by an increase in the efferent resistance which causes a compensatory increase in the filtration fraction and therefore a normal filtration rate. The reason for these modifications is not clear and it is impossible, even by a careful analysis of all the data, to draw a definite conclusion as to their nature. Some authors (16) affirm that these changes may be attributed, totally or partially, to some emotional factor, as for example, fear in the course of experiment, which is known to effect strongly the R. B. F., but we think that this interpretation is too simple and not very probable. The incidence of these changes (34, 37) in coarctation of the aorta is very much higher than the incidence of the fear reactions in patients studied with the same technique for other conditions. Moreover, our patients did not present the alarm syndrome described by Smith (55), but they remained still, throughout the experiment. Our interpretation is that these changes must be considered in the general pattern of changed arterial pressure (reduction of blood flow and of pulse pressure) below the stenosis, the increase of renal efferent resistances and of the F. F. representing a compensatory mechanism which permits normal G. F. R. in face of reduced R. B. F.

But though having interpreted these data as significant of a «renal ischaemia», may we: (a) ascribe the genesis of hypertension to it and (b) liken the renal pattern observed by us in coarctation of the aorta to that characteristic of essential hypertension, as Friedman et al. (34) and Genest et al. (37) have done?

In regard to the first question, there is a considerable disagreement as to whether renal ischaemia per se is the initiating factor in renal hypertension. For example, Corcoran & Page (46) have found that renal dynamics may be normal in dogs made hypertensive by renal artery constriction or perinephritis. Alpert & Lilienthal (68) have found that a high protein diet increases the renal plasma flow and filtration rate in dogs with experimental hypertension in a manner which is indistinguishable from the normal animal, another fact which argues against renal ischaemia as the primary factor in the genesis of this type of hypertension. Moreover the studies of Rodbard & Katz (69), Stamler et al. (70, 71) on the depressor response to inflammation, have shown that the decrease in blood pressure, determined by inflammation, is not directly dependent upon the relief of renal ischaemia. Finally, Friedman et al. (72) as a conclusion of their experiences, infer that renal ischaemia is neither the initiating nor the maintaining factor in experimental hypertension.

With regard to the second question, our cases show a renal pattern that may be likened in some respects to that found in essential hypertension (36), namely a low R. P. F. and R. B. F., with an increase in F. F. and in renal arteriolar resistances.

However, we must remember that the most startling and distinctive change effected in the kidney by essential hypertension (56, 37, 73) is a decrease of the tubular excretory mass. This reduction of Tm_{PAH} would depend on a diminution of the specific excretory function of every tubule rather than on tubular obstruction or obliteration (Smith (55), pages 721—2). As a consequence, in essential hypertension the derived data GFR/Tm_{PAH} and RPF/Tm_{PAH} are remarkably and characteristically increased, R. P. F. and G. F. R. being much less effected than Tm_{PAH} . Therefore we, as Harris et al. (16), in the 5th case in which the R. B. F. and F. F. showed changes like those of essential hypertension, have measured also Tm_{PAH} , finding that Tm_{PAH} and GFR/Tm_{PAH} were normal and RPF/Tm_{PAH} decreased. Finally, in essential hypertension, the increase in the renal resistance involves mostly and characteristically the afferent segment (55, 61) while in our cases the increase affected more the efferent and venular segments. Therefore, we cannot liken the hypertensive renal pattern to that observed in these cases of coarctation of the aorta.

The post-operative study of our cases show that intervention, removing the mechanical conditions, is followed by a tendency to return to normal of the pressure modifications and of the alterations of renal resistance and by a return to normal of the renal function. Therefore, the pre-operative renal changes (a) are functional and not anatomical; (b) they are secondary to the general haemodynamic changes.

Conclusions.

The pre-operative diastolic hypertension verified in our patients as in the greater number of cases of coarctation of the aorta, shows that the genesis of this hypertension cannot be attributed only to mechanical conditions. Leaving undiscussed the theoretical question whether renal ischaemia may be the cause of essential hypertension (criticized by many authors) we have found that the diastolic hypertension in coarctation of the aorta cannot be explained by the renal alterations observed by us and other investigators. In fact: (a) these alterations were not constant, though the diastolic hypertension was constantly present in all cases; (b) they depended functionally on the mechanical conditions being corrected by their removal. Moreover, these renal changes cannot be likened to those observed in essential hypertension, because the tubular capacity was conserved and the segments in which the renal resistances were further increased, were the venular and efferent, not the afferent ones.

Our interpretation of these findings is that these renal changes, when they are present, must be considered as a part in the general haemodynamic pattern below the stenosis, characterized by changed arterial pressure and reduction of the blood flow. The increase in renal efferent resistances and in F. F. represents a compensatory mechanism, which permits normal G. F. R. in the face of the reduced R. B. F. From our data, however, we cannot determine the pathogenesis of all these reversible haemodynamic changes below the stenosis (in which we include the renal ones) and whether they depend on a neurogenic factor or on a humoral (not a renal) one.

Summary.

The authors report their pre-operative study of renal function in 5 cases of coarctation of the aorta and the post-operative study of 3 of them.

The systolic-diastolic hypertension in the upper limbs and the low systolic and low pulse pressure in the lower limbs tended to become normal after surgical intervention.

On the basis of the renal results, the authors have divided the patients into 2 groups according to whether the R. P. F., R. B. F. and F. F. are within the normal ranges or not. The first group was characterized by a R. P. F. and R. B. F. in the low normal ranges and by a slight increase of the efferent resistance and decrease of afferent resistance; all the other data were normal. The second group was characterized by a decrease in R. P. F. and R. B. F. and an increase in F. F. and in total renal resistances, more accentuated in the efferent and venular segments. The other functions (including in one case Tm_{PAH}) were normal. Surgical intervention normalized the renal conditions.

Though the diastolic hypertension shows that the genesis of hypertension in coarctation of the aorta cannot be ascribed to the mechanical block only, the authors believe that the renal pathogenesis must be excluded. In fact: (a) the renal changes were not constant, though the diastolic hypertension was constantly observed; (b) they were dependent (on a functional ground) on the mechanical conditions, being corrected by the surgical intervention which removed the obstacle. Finally, the renal changes observed cannot be likened to those of essential hypertension, because the tubular capacity is conserved and the segmental resistances more affected are the efferent and venular ones.

The genesis of these renal changes is discussed; the authors believe that they must be considered as a part of the general haemodynamic pattern below the stenosis but it cannot be determined whether they depend on neurogenic or humoral (not renal) agencies.

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References.

1. Blumgart, H. L., Lawrence, J. S. & Ernestene, A. C.: *Arch. Int. Med.* 47: 806, 1931. —
2. Lewis, T.: *Heart* 16: 205, 1933. — 3. Hull, E.: *Am. Heart J.* 35: 980, 1948. — 4. Bing, R. J., Handelsman, J. C., Campbell, J. A., Griswold, H. E. & Blalock, A.: *Ann. Surg.* 128: 803, 1948. — 5. Gupta, T. C. & Wiggers, C. J.: *Circulation* 3: 17, 1951. — 6. Steele, J. M. & Cohn, A. E.: *J. Clin. Invest.* 17: 514, 1938. — 7. Steele, J. M.: *J. Clin. Invest.* 20: 473, 1941. — 8. Pickering, G. W.: *Clin. Sc.* 2: 209, 1936. — 9. Wakim, K. G., Slaughter, O. L. & Clagett, O. T.: *Proc. Staff. Meet. Mayo Clin.* 23: 347, 1948. — 10. Prinzmetal, M. & Wilson, C.: *J. Clin. Invest.* 15: 63, 1936. — 11. Goldman, M. L. & Schroeder, H. A.: *Am. J. Med.* 7: 454, 1949. — 12. Woodbury, R. A., Murphey, E. E. & Hamilton, W. F.: *Arch. Int. Med.* 65: 752, 1940. — 13. Brown, G. E. Jr., Pollack, A. A., Clagett, O. T. & Wood, E. H.: *Proc. Staff. Meet. Mayo Clin.* 23: 129, 1948. — 14. Brown, G. E. Jr., Clagett,

- O. T., Burchell, H. B. & Wood, E. H.: *Proc. Staff. Meet. Mayo Clin.* 23: 352, 1948. — 15. Hallenbeck, G. A., Wood, E. H., Burchell, H. B. & Clagett, O. T.: *Surg., Gynec. & Obst.* 92: 75, 1951. — 16. Harris, J. S., Sealy, W. C. & De Maria, W.: *Am. J. Med.* 9: 734, 1950. — 17. Grollman, A. & Ferrigan, J. P. Jr.: *Arch. Int. Med.* 53: 35, 1934. — 18. Stewart, H. G. & Bailey, R. L. Jr.: *J. Clin. Invest.* 20: 145, 1941. — 19. Wang, H. H.: *Cardiologia* 15: 30, 1949. — 20. Kondo, B., Winsor, T., Raulston, B. O. & Kuroiwa, D.: *Am. Heart J.* 39: 306, 1950. — 21. Goldzieher, J. W., McMahon, H. E. & Goldzieher, M. A.: *Arch. Int. Med.* 88: 835, 1951. — 22. Fisher, E. R. & Corcoran, A. C.: *Arch. Int. Med.* 89: 943, 1952. — 23. Sealy, W. C. & McSwain, G. H.: *Surgery* 25: 451, 1949. — 24. Sealy, W. C.: *Proc. Soc. Exper. Biol. & Med.* 71: 174, 1949. — 25. Sealy, W. C., De Maria, W. & Harris, G.: *Surgery, Gynec. & Obst.* 90: 193, 1950. — 26. Crafoord, C. & Nylin, G.: *J. Thoracic Surg.* 14: 347, 1945. — 27. Gross, R. E.: *Surgery* 18: 673, 1945. — 28. Rytand, D. A.: *Proc. Soc. Exper. Biol. & Med.* 38: 10, 1938. — 29. Rytand, D. A.: *J. Clin. Invest.* 17: 391, 1938. — 30. Goldblatt, H. & Kahn, J. R.: *J. A. M. A.* 110: 686, 1938. — 31. Goldblatt, H., Kahn, G. & Hanzal, R. F.: *J. Exper. Med.* 69: 649, 1939. — 32. Page, I. H.: *Am. Heart J.* 19: 218, 1940. — 33. Scott, H. W. Jr. & Bahnson, H. T.: *Surgery* 30: 206, 1951. — 34. Friedman, M., Selzer, A. & Rosenblum, H.: *J. Clin. Invest.* 20: 107, 1941. — 35. Malizia, E.: *Progresso Med.* 8: 214, 1952. — 36. Goldring, W., Chasis, H., Ranges, H. A. & Smith, H. W.: *J. Clin. Invest.* 20: 637, 1941. — 37. Genest, G., Newman, E. V., Kattus, A. A., Sinclair-Smith, B. & Genecin, A.: *Bull. Johns Hopkins Hosp.* 83: 429, 1948. — 38. Smith, H. W.: *Harvey Lect.* 35: 167, 1940. — 39. Barker, H. C. & Clark, J. K.: *Bull. Am. Coll. Surg.* 35: 53, 1950. — 40. Campbell, M. & Suzman, S.: *Brit. Heart J.* 9: 186, 1947. — 41. Swan, H., Robertson, H. T. & Johnson, M. E.: *Surg., Gynec. & Obst.* 90: 568, 1950. — 42. Provenzale, L.: *Policlinico (Sez. Prat.)* 59: 42, 1952. — 43. Chasis, H., Redish, J., Goldring, W. & Ranges, H. A.: *J. Clin. Invest.* 24: 583, 1945. — 44. Corcoran, A. C. & Page, I. H.: *J. Lab. & Clin. Med.* 26: 1713, 1941. — 45. Schroeder, H. A. & Steele, J. M.: *J. Exper. Med.* 72: 707, 1940. — 46. Corcoran, A. C. & Page, I. H.: *Am. J. Physiol.* 135: 361, 1942. — 47. Mason, M. F., Robinson, C. S. & Blalock, A.: *J. Exper. Med.* 72: 289, 1940. — 48. Hohlstaedt, K. G. & Page, I. H.: *J. Exper. Med.* 72: 201, 1940. — 49. Page, I. H. & Corcoran, A. C.: *Experimental renal hypertension*. C. C. Thomas, Springfield, Ill., 1948. — 50. Ogden, E.: *Bull. New York Acad. Med.* 24: 561, 1948. — 51. Gross, R. E., Bill, A. H. Jr. & Peirce, E. C.: *Surg., Gynecol. & Obst.* 88: 689, 1949. — 52. Gross, R. E.: *Circulation* 1: 41, 1950. — 53. Swan, H., Maaske, C., Johnson, M. & Gover, R.: *Arch. Surg.* 61: 732, 1950. — 54. Corcoran, A. C., Taylor, R. D., Page, I. H.: *Ann. Int. Med.* 28: 560, 1948. — 55. Smith, H. W.: *The Kidney. Structure and function in health and disease*. Oxford Univ. Press, New York 1951. — 56. Smith, H. W., Goldring, W. & Chasis, H.: *J. Clin. Invest.* 17: 263, 1938. — 57. Harrison, H. E.: *Proc. Soc. Exper. Biol. & Med.* 49: 111, 1943. — 58. Alving, A. S., Rubin, J. & Miller, B. F.: *J. Biol. Chem.* 127: 609, 1939. — 59. Smith, H. W., Finkelstein, N., Aliminosa, L., Crawford, B. & Graber, M.: *J. Clin. Invest.* 24: 388, 1945. — 60. Smith, H. W.: *J. Clin. Invest.* 20: 631, 1941. — 61. Gomez, D. M.: *J. Clin. Invest.* 30: 1143, 1951. — 62. King, J. T.: *Arch. Int. Med.* 38: 69, 1926. — 63. King, J. T.: *Ann. Int. Med.* 10: 1802, 1937. — 64. Abbot, M. E.: *Am. Heart J.* 3: 392, 1928. — 65. Blackford, L.: *Ann. Int. Med.* 41: 702, 1928. — 66. Hogeman, O.: *Acta Med. Scand.* 132: suppl. 216 a, 1948. — 67. Goldring, W. & Chasis, H.: *Hypertension and hypertensive diseases*. The Commonwealth Fund, New York 1944. — 68. Alpert, L. K. & Lilienthal, J. L. Jr.: *Bull. Johns Hopkins Hosp.* 72: 274, 1943. — 69. Rodbard, S. & Katz, L. N.: *Am. Heart J.* 26: 114, 1943. — 70. Stamler, J., Katz, N. L. & Rodbard, S.: *J. Exper. Med.* 90: 511, 1949. — 71. Stamler, J., Rodbard, S. & Katz, L. M.: *Am. J. Physiol.* 160: 21, 1950. — 72. Friedman, M., Sugarman, H. & Selzer, A.: *Am. J. Physiol.* 134: 493, 1941. — 73. Melli, G. & Bartorelli, C.: *L'ipertensione essenziale. Relazione al 51 Congresso della Soc. It. Med. Interna*, Pozzi ed., Roma 1951. — 74. Hamburger, J. & Ryckewaert, A.: *Nouveaux procédés d'exploration fonctionnelle du rein*. Flammarion ed., Paris 1949.

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Hypopotassemia in Hyperparathyroidism.

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An increasing interest in hyperparathyroidism is to be noted ever since the middle of the 1920's. In Sweden, the diagnostics, therapy and prognosis of hyperparathyroidism were closely studied by Hellström. In 1947, Norris made a compilation of no less than 322 cases. He ends up by declaring that, at least during the following ten-year-period, every case of hyperparathyroidism (hp.) should be published in order to render possible a recognition of all the diverse forms in which this disease may manifest itself.

It is not my intention to account for this disease as a whole (see, *e. g.*, Hellström 1950, Norris 1947), only to present some views on the subject because of a recently treated case that may have some general interest.

Hospital Record No. 790/1952. T. W. A female, born in 1885, who had been healthy and fit for work all her life, except for an operation owing to renal calculi on the right side in 1934, and on the left side in 1941 (on both occasions nephrolithotomy). In 1947, onset of articular troubles and pyrexia. Her condition was interpreted as a rheumatic fever and she was nursed at home for 8 months. According to her own statement, she had had no swollen joints, but a severe pain in the joints and musculature. In the Autumn of 1949, a renewed phase of pains, and likewise in 1950. Admitted to home district hospital in 1950 under the following diagnosis: polyarthritis chron. + cystitis chron. At the time she suffered from a slightly restricted ability to move the knee joints and crepitations. No tenderness nor restricted mobility in the other joints. Sedimentation rate: 61 mm/hour, non-protein nitrogen 47 mg % and a positive Heller reaction. After this she was nursed at a home for convalescents under the same diagnosis. Slight improvement from physical therapeutics. Readmitted to home district hospital in the Spring of 1951. Again suffering from articular pains without any swelling or restricted mobility. Slightly elevated blood pressure (170/90), a high sedimentation rate (83 mm/hour) and albumen in urine. Myelomatosis is suspected though not verifiable. Blood calcium 12.3 mg %. Diagnosis: polyarthritis chron. + nephritis chron. + osteoporosis.

The patient was admitted to the Medical Clinic of the Caroline Hospital in April, 1952. She had, during the past year, been confined to bed owing to pains and weakness in the joints, and had been unable to use her legs. She had throughout a subfebrile temperature. On and off infections in the urinary tract. Sluggish evacuation. No cardiac

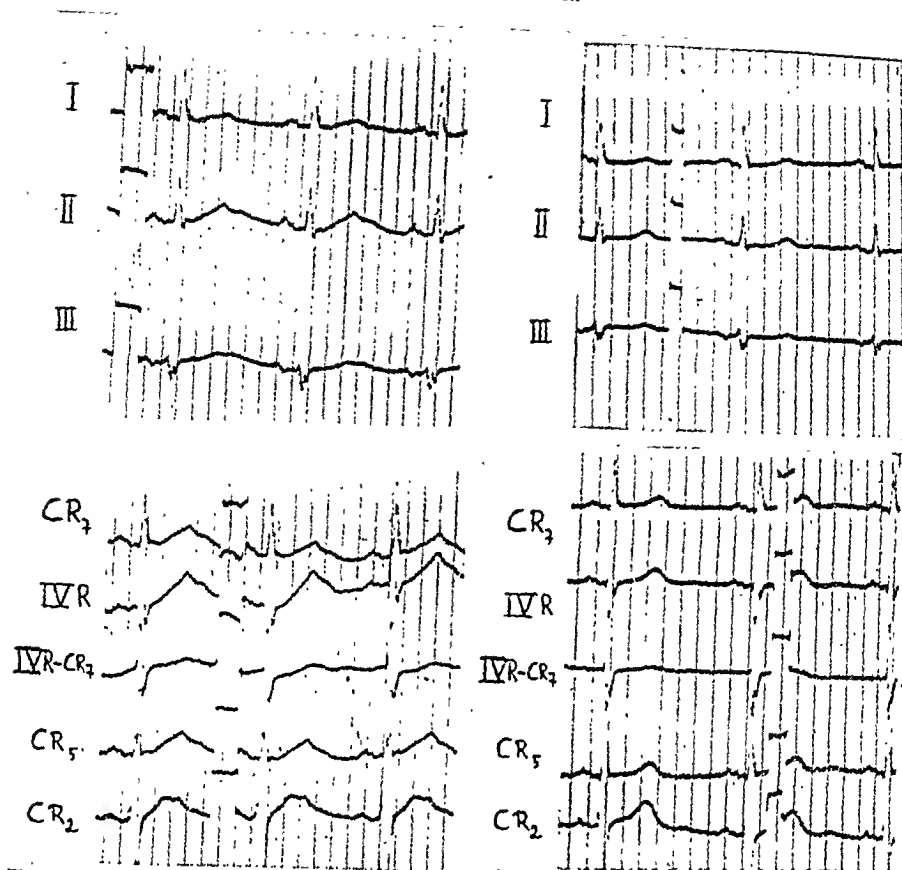


Fig. 1. ECG before (left) and after (right) the operation.

troubles. At the admission, the patient was tired and weak, being hardly able to speak and concentrate. Nevertheless, she knew her whereabouts and was mentally clear. Unable to stand on her legs and almost too weak to move in bed. Physical examination: Normal heart. Blood pressure 155/80. Normal lungs, abdomen and reflexes. The joints: at palpation a tenderness in the right wrist as well as round the knee joints. No swollen joints, no restricted mobility. No faulty positions. Laboratory findings: Temp. 37.7° C, sedimentation rate 45 mm/hour. Blood: Hb 70 %, RBC 3.30 million. WBC 19,300 with normal diff. Urine: Heller positive. Esbach not registrable. Urinary sediment: abundance of white blood corpuscles, otherwise nothing noteworthy. Spec. gravity 1,010. NPN 58 mg %. Negative agglutination reaction for polyarthritis. AST and asta without remark.

Lung X-rays showed minor bronchopneumonic densities basally on the left side. It was decided to deal with them and the infection in the urinary tract first, but the patient found it difficult to tolerate sulfa and antibiotics. She was subject to strange spells of weakness when she suddenly appeared »worn out», mentally as well as physically. These so-called fits occurred for no obvious reason, often several times daily.

Continued examination revealed a general marked osteoporosis of the skeleton, but no roentgenologic signs of polyarthritis, also an ECG such as is seen in hypopotassemia and hypercalcemia (Sjöstrand 1951, Carlsten 1953) (see Fig. 1).

A closer analysis of the blood electrolytes gave the following values: Potassium 12.5 mg %, calcium 15 mg %, sodium 336 mg %, phosphorus 6.1 mg % and alkali reserve 23 mmol HCO_3 .

Firstly, potassium acetate was administered per os at a dosage of 3 g/daily, and considerably improved her general condition. Also the ECG changes were temporarily normalized after a single dose of 10 g. KCL per os (cp. Carlsten, where the ECG-changes are reported in detail).

A check-up of the blood calcium value showed 14 mg %.

The history of renal calculi and the renal injury, osteoporosis, adynamia and the high calcium value in the blood present a picture of hyperparathyroidism. Surgery was proposed in spite of the severe renal injury with continuous albuminuria and strongly reduced capacity to concentrate (spec. gravity 1,009—1,013) as well as an elevated non-protein nitrogen (between 50 and 70 mg %). At the operation, performed by Professor Hellström on July 4th, 1952, a parathyroid adenoma, the size of a Brazil-nut, was removed from the left side. Patho-anatomic diagnosis (Lindberg) disclosed a parathyroid adenoma consisting largely of main cells without any sign of malignancy.

In the after-course, low calcium values and convulsions. The administration of calcium and fortedol caused a gradual normalization of her condition. After physical therapeutics, the patient could be discharged in the beginning of October 1952. She could then be up and about without much inconvenience.

At a control examination in March 1953, she had a non-protein nitrogen value of 104 mg % after an infection in the air passages. This value went down to 50 mg % after hospitalization. Heller was positive. Blood pressure 160/90. Blood calcium 10.9—11.8 mg %. Blood potassium 15.3 mg %. Sedimentation rate 61 mm. She was up and able to take care of herself and to go for short walks outdoors.

Summary:

The report concerns a female of 67 years who had been operated upon twice before for renal calculi, and had been subjected to articular troubles more than 5 years after the last surgical intervention. Her joints were neither swollen nor deformed, but painful when moved and tender at palpation. She had a high sedimentation rate and occasionally an elevated temperature, and had several turns of hospitalization under a diagnosis of rheumatic fever and chronic polyarthritis. She was admitted to the Caroline Hospital, after having been confined to bed for a year without being able to stand on her legs. A general osteoporosis and high sedimentation rate were observed as well as renal injury, but no signs of a polyarthritis. On the other hand, a severe electrolytic disturbance was noted, ascertained at closer analysis as due to hyperparathyroidism. She was subjected to an operation in spite of unsatisfactory renal function, a parathyroid adenoma being removed. After a few months, she was discharged as much improved and up and able to take care of herself.

Discussion.

The prognosis of hp. is highly dependent on an early diagnosis so that surgery can be performed before the organ changes have become irreversible. As emphasized by Hellström, the extent of the renal injury is decisive in this connection, while the skeletal changes seem to be of a subordinate significance.

The symptoms in hp. are generally classified in three groups: 1) skeletal symptoms, 2) urinary tract symptoms, and 3) general symptoms due to hypercalcemia.

Especially the cases referring to group 2 (*i. e.* those with renal injury) are nowadays more often diagnosed early on account of the general knowledge that renal calculi, often bilateral and recidivating, are common manifestations of hp.

As to the cases with skeletal symptoms, at an early stage of the disease a typical osteitis fibrosa generalisata is not to be expected. These must be regarded as advanced cases, and seem to have become more and more rare in the past few years. The early symptoms from the skeleton are uncharacteristic. D. Barr (1947) writes in the Oxford Medicine that the most constant symptom is a pain localized to bones and joints and that this pain can simulate an early arthritis. Perrow (1950) states that the usual symptom is articular pains, generally in the form of a moderate ache in the back and hips. Further, the muscular weakness is typical. An X-ray examination of the skeleton reveals a diffuse decalcification, as a rule without any special characteristics.

An ache in the joints and muscles, weakness and difficulty in moving, as well as a skeletal decalcification are all symptoms usually connected with a chronic polyarthritis or arthrosis.

An osteoporotic form of hp. may therefore in many respects resemble an early rheumatoid arthritis or arthrosis. This particular case had in fact been remitted as a subchronic polyarthritis, and the same applies to many other cases reported in the literature.

This resemblance to the symptom complex of rheumatoid arthritis has been pointed out earlier (particularly in reports on hp., but less frequently, if at all, in descriptions of rheumatic conditions). Still, in my opinion this must again be emphasized. Just as nowadays an increasing number of hp. cases are detected among those suffering from renal calculi, an intensified attention to the possibility of this differential diagnosis, should result in the finding of some cases of an early hp., while still amenable to radical surgery, from the large group of patients with unidentified joint troubles.

It may be of interest to note that the rôle of the parathyroid in the origination of the genuine rheumatoid arthritis has been discussed, and that even parathyroidectomy has been resorted to in cases of rheumatoid arthritis without any signs of hp. In 1949, Lièvre gave an account of this question. He concluded, however, that the successful cases submitted to this operation do not justify the assumption that hp. should be the cause of any case of genuine rheumatoid arthritis.

Another point of interest in the present case is the electrolytic disturbance. The patient had hypopotassemia at admission, with ECG changes and typical clinical manifestations, *viz.*, pronounced muscular hypotonia and weakness, as well as mental asthenia with difficulty to concentrate. Her condition improved considerably through the administration of potassium per os. After the operation, when the serum-calcium value had been normalized, she showed a normal serum potassium value and a normal ECG and likewise at follow-up examination nine months later.

What was the reason for this hypopotassemia? Prior to her admission the patient had had no pathologic fluid losses, such as vomiting fits, diarrhoea, etc., and had a normal diet. Nor had she of late obtained any form of medicinal treatment.

The hypopotassemia must then be attributed to the basic disease, hyperparathyroidism, whether directly or via the renal injury.

As the patient, in spite of no change in the inadequate renal function, disclosed a normal serum-potassium value after the intervention, the renal injury was probably of no significance in this connection.

Normal neuromuscular excitability and normal cardiac activity, etc., call for a normal relation between the potassium and calcium ions (as well as other ions). Potassium and calcium are in several instances antagonists in regard to their physiologic effect. Potassium yields ECG-changes, at too high as well as at too low serum values, and effects the excitability of the nervous system. Hypocalcemia has a typical ECG and leads to tetany, whereas hypercalcemia causes but slight ECG changes and has no effect on the nervous system (Anning 1948, Merrill 1952). A probably genuine hyperealcemia can be studied at calciferol poisoning. The most usual symptoms in this disease are thirst and a lack of appetite, vomiting and fatigue (Anning et al. 1948), while none of Anning's 35 patients with toxic symptoms manifested a muscular hypotonia.

Muscular weakness, hypotonia (adynamia) and mental asthenia are, as is known, symptoms typical of hp. and are, as a rule, attributed to the hypercalcemia as such. However, this does not agree with the observations made in cases with calciferol poisoning, nor with theoretical expectations. I should therefore, on the basis of the present case, suggest that these symptoms of hp. may, conceivably, be due to a hypopotassemia, being a part symptom of the electrolytic disturbance in hp. I have only in one instance of hp. in the literature found recorded values of serum potassium which in that case were low (between 3 and 4 mekv/lit).

A hypopotassemia in hp. might even conform to the mental asthenia and, perhaps, with the more serious mental symptoms described in a few cases (ep. Nord. Med. 1953, 49: 723). Eitinger (1942) gives an account of a case of his own and reports 7 cases from the literature. He states that the mental symptoms in hp. are uncharacteristic, drowsiness and slackness being common to most of them (in 7 out of 8 cases) as well as dullness (in 4 out of 8 cases). The behaviour of the woman under his observation entirely agreed with that of my patient before operation. Also Oliver (1939) and Fitz & Hallman (1952) report similar cases. They all have in common a complete mental recovery after the surgical intervention.

As may be seen, these pictures conform in the majority of cases with what is to be noted in hypopotassemia.

Summary.

One case of hyperparathyroidism in an elderly woman is described.

It is pointed out that these cases are often for a long time misinterpreted as rheumatic diseases.

The present case had a pronounced hypopotassemia. The question whether a hypopotassemia can be a part symptom in hyperparathyroidism and whether it be at the bottom of some of the physical as well as mental symptoms is discussed.

Literature.

Anning, S. T. et al.: *Quart. J. Med.* 1948, 17; 203. — Barr, D.: *Oxford Medicine* 1947, vol. III, part II, page 838. — Carlsten, A.: *Acta Med. Scand.* 1953, 146; 424. — E. L.: *Nord. Med.* 1953, 49; 723. — Eitinger, L.: *Nord. Med.* 1942, 14; 1581. — Fenn, W. O.: *Physiol. Reviews* 1940, 20; 377. — Finck, C. et al.: *Am. J. Med.* 1946, 1; 337. — Fitz, T. & Hallman, B.: *Arch. Int. Med.* 1952, 89; 547. — Hellström, J.: *Acta Chir. Scand.* 1950, 100; 391. — Hellström, J.: *Nord. Med.* 1951, 45; 263. — Lièvre, J.-A.: *Revue du Rhumatisme* 1949, 16; 447. — Merrill, A.: *Am. Heart Journ.* 1952, 43; 634. — Norris, E. H.: *Int. Abstr. Surg.* 1947, 84; 1. — Oliver, W. A.: *Lancet* 1939, 2; 240. — Perrow, J. B. S.: *Virginia M. Month.* 1950, 77; 646. — Sjöstrand, T.: *Acta Physiol. Scand.* 1951, 24; 274. — Tarail, R. & Elkinton, R.: *J. Clin. Invest.* 1949, 28; 99.

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Suprasternal Puncture of the Left Atrium for Flow Studies.

By

STIG RADNER.

(Submitted for publication August 18, 1953.)

Suprasternal puncture of the thoracic aorta is being used as a routine method in our laboratory for studying the *outflow* hemodynamics of the left heart. The technique was described by the present author in 1953.

While performing aortic punctures, the needle was occasionally passed through the space between the aorta and the trachea. At the bottom of this space the resistance of the left atrium might be felt and its cavity punctured.

Post mortem studies were performed on more than fifty corpses, with thoracic organs left in situ, and the left atrium was found to be accessible for direct puncture from the suprasternal fossa in all of the cases. After the anatomical studies had been completed, the present technique of left atrial puncture was applied in living subjects for investigating the *inflow* hemodynamics of the left heart.

Anatomical Notes.

The left atrium is situated in the midline, crucified by its venous extremities in the pulmonary hili, and surrounded by two sets of tubular structures and cavities (Fig. 1). The main bronchi straddle over its posterior part, and between the bronchi it is curtained by the descending aorta, the oesophagus and the right pleural cavity — the posterior relations. The anterior part of the left atrium is embraced by the ascending aorta, the bifurcating pulmonary artery, the superior vena cava and the right atrium — the anterior relations. Between the two groups of structures there is a space which permits the extrapleural and extratubular approach to the left atrium from the suprasternal notch. The transverse sinus of the pericardial sac covers the upper part of the atrium behind the pulmonary artery, and puncture is made through the sinus in most cases.

Suprasternal Needle.

A special double needle is used (Fig. 2). It consists of an outer needle attached to a three-way tube, and an inner needle which is inserted into the outer through

this tube. The internal diameter of the inner needle is 0.25 mm, and same diameter of the outer is 0.60; the external diameter of the outer needle is 0.80 mm. The sharp tip of the inner needle projects for about 2 mm outside the outer, which is obliquely cut and streamlined. The free length of the outer needle is 165 mm.

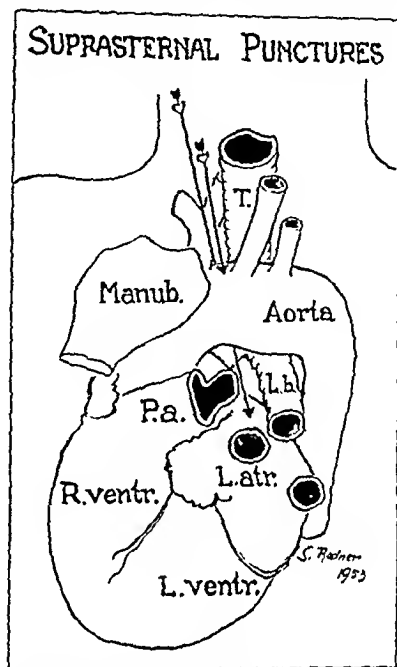


Fig. 1. Drawing to show the anatomical relationships of the left atrium. Arrows indicate the direction of suprasternal punctures of the aorta and the left atrium. T. = Trachea. L. b. = Left main bronchus. P. a. = Pulmonary artery, cut to show first part of its right branch.

The three-way tube has one stop-cock on each limb to permit infusion, aspiration and pressure measurement through the outer needle. For recording pressures, its proximal straight limb is connected with a Tybjaerg Hansen manometer by means of a short piece of a Courmand catheter No. 7, and a canalized bayonet knob. Before puncturing, a one cc syringe is attached to the inner needle for flushing and aspiration.

Technique.

Premedication is not necessary. The patient is placed in a supine position, with the head bent slightly backwards and turned to the left. Local anaesthetic without adrenalin is injected from the point of entrance through the skin in front of the trachea, and towards the aortic arch, but not below this level. The double needle is inserted in the midline 3—4 cm above the upper border of the sternum; if it is inserted into the bottom of the suprasternal notch the skin forms a pursing funnel around it.

The needle is directed along the anterior border of the trachea, and posteriorly

to the aortic arch which is felt pulsating at a depth of about 1—6 cm below the suprasternal fossa. A slight digital pressure on the trachea may be necessary to guide the needle into the desired space. Here the needle goes smoothly downwards and, passing the tracheal bifurcation, it reaches a membranous and softly pulsating resistance at a depth of about 8—16 cm. This is punctured, and blood is

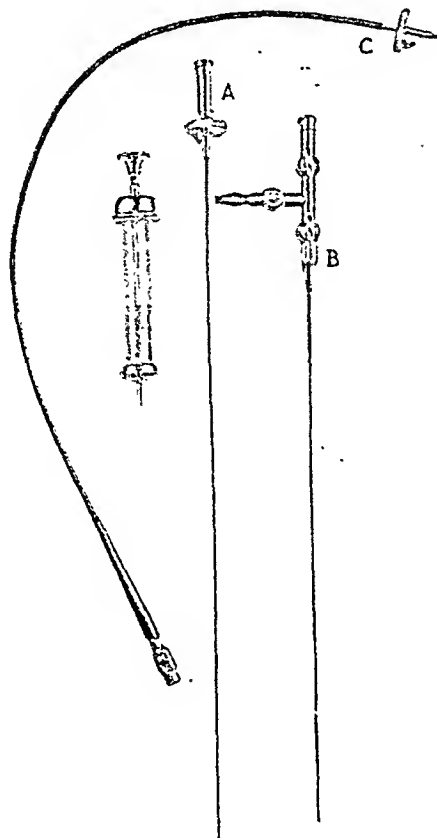


Fig. 2. Suprasternal needle with accessories. A = Inner needle with bayonet knob for the outer needle, and fitting for syringe or canalized knob of catheter. B = Outer needle attached to three-way tube. Infusion of saline solution from pressure bottle through rubber tubing connected with transverse limb of three-way tube. C = Catheter with canalized bayonet knob for straight limb of three-way tube or for fitting of the inner needle.

aspirated through the inner needle to determine its position; same determination may be achieved by pressure measurement, although damping prevents accurate recordings to be taken through the small caliber of the inner needle. Flow studies are made through the outer needle, after the inner has been withdrawn.

Results.

Suprasternal puncture of the left atrium was performed in five cases for flow studies. No complications were encountered. Although no premedication was

given, the puncture was almost painless. One example of the pressure curves obtained from the left atrium is shown (Fig. 3).

Our material is small so far, but it was considered sufficiently large to confirm clinically our post mortem experiences, which, in turn, seem to form a reliable anatomical basis for continued routine use of the method.

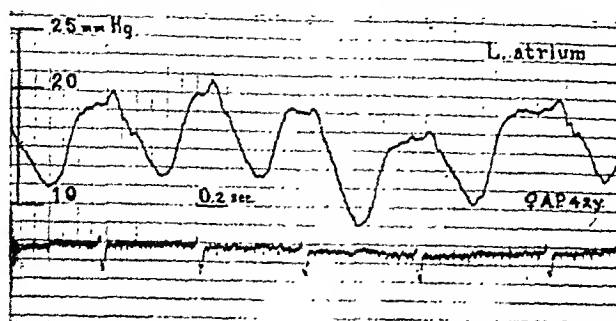


Fig. 3. Left atrial pressure curve obtained with the present technique in a case of pure mitral stenosis.

Comments.

Information of the flow characteristics of the left atrium is of primary interest for the surgical management of cardiac disease. The pulmonary wedge pressure curves are widely used as an indirect way of obtaining such information. It has been repeatedly observed, however, that the wedge pressure does not constantly represent an accurate reflection of the left atrial pressure. Direct methods of pressure measurements therefore have been proposed. In 1953 Allison and Linden suggested the »bronchoscopic measurement of the left auricular pressure»; the atrium was punctured through one of the main bronchi. In the same year V. O. Björk tried a paravertebral access to the atrium; a needle was introduced percutaneously through an intercostal space at the atrial level. Additional experience with the two methods seems to be needed before conclusions can be drawn as to their usefulness for routine work.

Summary.

A new technique of direct puncture of the left atrium was applied in five cases. The puncture was made with a special needle from the suprasternal fossa through the space between the trachea and the aortic arch. No complications were encountered.

References.

- Allison, P. R., and Linden, R. J.: »The Bronchoscopic Measurement of Left Auricular Pressure», *Circulation*, Vol. 7, p. 669. — Björk, V. O.: Unpublished observations, 1953. — Radner, S.: »Method for Recording Aortic Pressure Pulses», *Scand. Journ. Clin. and Laborat. Invest.*, 1953, in press.

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Does Rapid Dehydration in Cardiac Decompensation Produce Thromboembolic Complications?

By

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(Submitted for publication August 19, 1953.)

The aim of the present investigation has been to ascertain the frequency of thrombosis and embolism in rapid dehydration in cardiac decompensation cases.

The risk of thrombosis in old bedridden patients with heart disease is well known. It is possible that a very intensive therapy with rapid dehydration may augment the tendency to thrombosis.

The therapeutic means of treating the decompensation are confinement to bed, oxygen, a salt-poor diet, digitalis, purine derivatives, and mercurials, possibly combined with intermittent acidosis therapy. The two extremes in the principle of treatment are (1) conservative treatment, where bed rest, a salt-poor diet, and perhaps digitalis by mouth cause dehydration. A large amount of edema fluid may be excreted in this way. (2) Active treatment, in which the body is quickly saturated with cedilanide intravenously, and during the first few days, mercury diuretics are injected intravenously in addition to the therapy mentioned under (1).

The first-mentioned treatment causes gradually increasing urine output in the course of 4—7 days (in some few cases up to more than 3 litres daily). In the second type of treatment a rapid, sometimes violent, increase in urine output occurs in the first few days, followed by considerable fluctuations of fluid loss. Nausea, sometimes vomiting and diarrhea after the intensive therapy will further cause changes in the electrolytic and viscosity conditions of the blood.

About the mode of action of the drugs little need be said. The chief action of the digitalis preparations is on the heart. Cedilanide injections do not primarily increase filtration or salt excretion. Mercury diuretics have the effect of enzyme poisoning in the renal tubules, lowering the absorption of chlorine, sodium, potassium, and magnesium. The filtration rate does not improve primarily, and is reduced by overdosing. The purine derivatives increase the rate of filtration.

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The general minor effects of these drugs will not be discussed here. This paper is concerned with the question of how a really intensive therapy can be conceived to cause thrombosis and embolism.

Three main factors are of importance in the causation of thrombotic vascular phenomena: local vascular changes, lowered rate of circulation (which cannot alone cause the thromboses), and changes in the viscosity and mechanism of coagulation of the blood. The two latter factors are probably the most important.

The various authors disagree as to the primary cause of the thrombosis. They use divers, often inaccurate, methods in their investigations. In addition, there remain factors in the pathogenesis of the thrombosis which have not been investigated.

Russek and Zohman have correlated the risk of thrombosis with the amount of fluid lost. S. Pere showed that novurite causes a reduction of the coagulation time of the blood which is proportional to the diuresis product. Marvel and Shulenberg think that a rapid output of large volumes of fluid increases the risk of thrombosis and embolism. Hemoconcentration and increased viscosity (perhaps also electrolytic changes) must here play a part.

Other authors attribute to digitalis and the mercurial compounds a direct influence on the coagulation of the blood. De Takats et al. state that digitalis acts as an antiheparin, Massy et al. that digitalis reduces the coagulation time, Secher that digitoxin shortens the coagulation time in vitro in normal patients.

Macht found (in experiments on animals) that mercury diuretics had a pronounced »thromboplastic» effect. Pere thinks that it is presumably due to a seeping of thromboplastinogen (not measured) into the bloodstream which favours the mechanism of coagulation.

Beaumont and Lenègre consider combined treatment with digitalis and mercurial diuretics risky. Among 26 patients they found 14 cases with thromboembolic complications. Six were fatal. The patients had an increased heparin tolerance test.

Thus there exist a series of papers which would seem to indicate that rapid compensation may favour the occurrence of thrombosis either by altering the viscosity of the blood through rapid dehydration or by the administration of drugs which directly affect the mechanism of coagulation. Perhaps both factors are of importance.

The Author's Series of Cases. Surviving Patients.

In order to judge the practical importance of the problem I have examined the case records and ascertained the number of thromboembolic complications in two differently treated groups of cases of cardiac decompensation. One group from Frederiksberg Hospital, Medical Department E (F.H. = (I)) was treated on more active lines, the other group from Svendborg Central Hospital (Sv.C.H. = (II)) was treated very conservatively. The case notes were obtained by going through, in their chronological order, all cases of mb. cordis, decomp. cordis (the main diagnosis) in 1951—52, up to a number of about 100 from each department. Patients suffering from thromboembolic complications on admission were not

included, not were cases of coronary thrombosis, or patients admitted in a moribund condition (3—4 in each of the series).

The material from F.H. (I) totalled 116 (80 survivors + 36 fatal cases), from Sv.C.H. (II) 99 (79 survivors + 20 fatal cases, see below).

The patients from F.H. were elderly, several had been treated at home, and several had previously been admitted to hospital. This gives no indication as to the gravity of the disease. Many had received quite inadequate treatment at home. A rough estimate of the duration of the disease shows no conclusive difference (Table 1).

A tentative classification of the type of heart disease was made by means of the history, physical examination, X-ray, electrocardiograms etc. (Table 2.) In several cases it was impossible to do this quite correctly. The term »insufficiencia cordis» is somewhat vague. In the greater number of cases the condition was due to arteriosclerosis, and in some to infection. If the patients had myocardial degeneration + hypertension they were included in the group with hypertension. The figures are astonishingly uniform, the distribution being the usual one.

Table 1.
Surviving Decompensated Heart-patients.

	I	Thromboembolic compl.	II
Total	80		79
Male	40	11 } 26	45
Female	40	15 }	34
Average age	67		63.5
Average age for patients with complications	67		
Duration of illness			
< 1 year	23	7 }	19
1—5 »	26	9 }	21
5—10 »	14	7 }	21
> 10 »	17	3 }	18
Previously admitted to hospital ..	17		12
Treated at home	53		23

Group I = F.H., group II = Sv.C.H.

There were no thromboembolic complications among patients from Sv.C.H. 32 % of the patients from F.H. had thromboembolic complications.

Table 2.
Classification of Heart Disease. Thromboembolic Complications.

	I		Thromboembolic complications	II	
	♀	♂		♀	♂
Insufficiencia cordis	15	16	13	12	25
Hypertensio arterialis	9	13	7	10	11
Stenosis mitralis	10	3	3	8	5
Chronic cor pulm.	5	4	3	3	2
Vitium valv. aortae	0	2	0	0	2
Thrombosis a. coron. seqv.	1	2	0	1	0

It is difficult to obtain an expression of the degree of severity of the patients' disease. All patients were suffering from cardiac decompensation. I have chosen to divide them according to the degree of decompensation, and given points for the degree of pulmonary stasis, hepatic stasis and peripheral edema as revealed by the physical examination, slight stasis or edema receiving 1, moderate stasis 2, and marked stasis 3 points. The three figures are added up. Then the material is divided into 3 main groups: Decompensation group I with 1—3 points, group II with 4—6, group III with 7—9 points. Table 3 shows the distribution of the cases according to this method. Perhaps the condition of the patients from F.H. was a little worse.

The number of patients with febrile complications and fixed arrhythmia on admission to hospital and the number of patients with reduced kidney function were essentially the same in either series.

Table 3.
Graduation of Illness. Thromboembolic Complications.

	I	Complications	II
<i>Graduation of decompensation</i>			
I	35	11	42
II	38	13	25
III	7	2	12
Fixed arrhythmia + deficit	20	7	24
— deficit	27	7	21
Impaired renal function	10	0	4
Febrile complications	7	4	8

Judged by degree of illness there is no decisive difference.

Among the febrile complications are not included maximum temperatures of 38° if they became normal quickly without any treatment other than that of increasing the urine output.

The renal function was not more closely investigated. In the group «reduced renal function» were included cases with a maximum specific gravity of the urine of 1,016, and/or blood urea about 50 mg% if the figures did not return to normal during the period of compensation. These values were chosen for purely practical reasons, they show fair agreement with the clinical results, and the requirements of several modern American cardiologists, among others W. E. Judson. Most of the increased blood urea values ranged from 50 to 80 mg% which is not unusual in a case of cardiac decompensation. Few figures exhibited a further rise during treatment. If the primary condition seemed to be renal in origin the case was not included in the series. There were several patients with increased blood urea from F.H., perhaps latent in cases of low salt syndromes.

The intensity of the treatment is divided into groups in table 4. The distribution of the cases over these is typical. Roughly it may be said that the intensity of treatment in the two hospitals each represents its extreme. It must be added with reference to group IV that the digitalis treatment was quicker at F.H. just as the

Table 4.

*Groups of Treatment, Distribution of Patients. Thromboembolic Complications.**Thromboembolic complications.*

	I	Complie.	II
I) Patients treated in the first and/or the second 24 hours with cedilanide (strophanthin) and mercurial diuretics intravenously	24	15	0
II) Treated in the first or second 24 hours with cedilanide (strophanthin) intravenously	4	2	2
III) Treated in the first or second 24 hours with mercurial diuretics intravenously and digitalis perorally	6	2	0
IV) Saturated with digitalis perorally later mercurial diuretics intravenously	37	5	15
V) Treated later with mercurial diuretics, — digitalis	7	1	4
VI) Treated with digitalis perorally, — mercurial diuretics	2	1	35
VII) Treated without digitalis and without mercurial diuretics	0	0	23

Table 5.

Maximum Urine Output.

	I	Complic.	II
< 1,000 cc	6	0	30
1,000—1,500 "	12	4	18
1,500—2,000 "	18	6	11
2,000—2,500 "	18	6	8 No
2,500—3,000 "	9	3	3 compli-
3,000—3,500 "	9	4	2 cations
3,500—4,000 "	2	1	5
4,000—4,500 "	3	0	1
4,500—5,000 "	1	0	1
7,000 "	1	1	

treatment with mercurial diuretics was started earlier, was more intense, with more frequent injections (not more frequently than every 5 days) and larger doses usually 2 cc). The cedilanide dosage was of the usual kind.

In both hospitals the diet was salt-poor with slightly reduced intake of liquid food.

In both, patients were fairly soon permitted to go to the lavatory or use a bedpan chair. At Sv.C.H. they became ambulatory a little later.

No exact information about the balance of fluids can be given. Many patients from F.H. suffered considerable loss of fluid after intensive therapy owing to nausea, vomiting, and diarrhea.

Table 5 shows maximum urine output. The values are distinctly higher at F.H. where only 6 patients have less than 1 litre, while at Sv.C.H. there are 30. Patients at F.H. remained in hospital an average of 28 days, at Sv.C.H. of 44 days.

Thromboembolic Complications in Surviving Patients.

These are peripheral phlebothromboses and thrombophlebitis, as well as thromboembolic phenomena of the lungs, brain, and kidneys. Three-fourths of the patients with diagnosed pulmonary infarction had typical bloody expectorate. (A large number of the pulmonary infarcts in cases of cardiac decompensation are not diagnosed. On post-mortem of 234 heart patients Hines and Hunt found — in a mixed material — that 34.6 % had pulmonary infarction; but only a few had been diagnosed in vivo). In this material the complication most frequently occurred

Table 6.

Thromboembolic Complications in Surviving Decompensated Heart-patients.

I: 29 complications in 26 patients = 32 % of 80 survivals. (F.H.)

II: No complications.

	I	
	♀	♂
<i>Pulmonary infarct.</i>	5	7
<i>Thrombophlebit.</i>	8	1
<i>Renal infarct.</i>	1	2
<i>Splenic infarct.</i>	1	0
<i>Cerebral accident</i>	1	1
<i>Febrile during treatment</i>	1	1

Group I: 32 % had thromboembolic complications.
15 % had pulmonary infarction.

at a time when the patient showed distinct signs of recovery. The findings on auscultation were plain, and the patients had had a raised temperature for about a week, without any improvement after injection of penicillin.

Renal infarction had been diagnosed on the following symptoms: Sudden pain in the renal region with macroscopically bloody urine, followed by normal findings, and no clinical signs of any other etiology. (Cases of only microscopical hematuria have not been included.)

A slight febrile reaction during treatment with mercurial diuretics is frequent. Sometimes a more pronounced pyrexia of longer duration is seen, which disappears only after discontinuation of treatment. Autopsy of such cases which terminate fatally usually shows a deep thrombophlebitis, *e. g.* in the minor pelvis, as a possible explanation of the fever. 2 patients of this type were included.

The distribution of the complications appears in Table 6. About 32 % of the patients from F.H. developed complications. About 15 % had pulmonary infarction, about 10 % peripheral phlebitis. These figures reach the upper limit of the values given for the various complication. (It was not possible to find material which was comparable with that from F.H.) There were no complications among the survivors from Sv.C.H.

The relationship of the complications to the classification of the disease, the sex, age, duration of disease, renal function, febrile complications and fixed arrhythmia showed nothing out of the ordinary. There was no conclusive correlation between the amount of the urine output and the frequency of the complications

(Table 5), the complications did not occur with particular frequency in the most severe cases (Table 3).

On the other hand, there was a correlation between the number of the complications and the intensity of the treatment (Table 4). If the explanation were that those who had received the most intensive treatment were the most affected, and that this was the cause of the complications, more cases would be found among the most severely affected groups, and at any rate some in the material from Sv.C.H.

Conclusion: So far as can be seen, the two groups are comparable. The patients from F.H. were a little older, perhaps a little more ill, than the patients from Sv.C.H., but since the complications did not occur especially among the oldest or the most severely affected this is of no decisive importance. 32 % of the patients from F.H. developed complications, 15 % pulmonary infarction. There is a correlation between the intensity of the treatment and the frequency of the complications, but no unmistakable correlation between the latter and the volume of urine passed.

The Fatal Cases.

It is possible that the more intensive therapy saves several patients who would otherwise die. In order to obtain some idea of this I have gone through the post-mortem diagnoses for the fatal cardiac decompensation cases in the same period. Patients were omitted who upon admission had coronary thrombosis, thromboembolic complications, or were beyond the reach of therapy. Patients who died from other causes, *e. g.* cancer, were not included. The postmortem diagnoses from Sv.C.H. were included from the time when the Hospital had a prosector. There were 20 fatal cases (about 24 %) and 64 survivors in the same period; 8 % died of pulmonary embolism.

Table 7.

Dead Decompensated Heart-patients. Diagnosis at autopsy.

I: 36 in 116 = about 31 % dead.

II: 20 in 84 = about 24 % dead.

	I	II
<i>Pulmonary embolism</i>	13	7
» — <i>autopsy</i>	3	
» <i>Valvular disease</i>	7	2
» — <i>autopsy</i>		2
» <i>Enlarged heart</i>	6	3
<i>Luetic aortitis</i>	2	2
<i>Chronic cor pulm.</i>	2	1
<i>Symphysis pericardii</i>	1	1
<i>Healed coronary thrombosis</i>	1 + 1	2

Group I: 31 % dead, 14 % had a fatal pulmonary infarct.

Group II: 24 % dead, 8 % had fatal pulmonary infarction.

¹ The autopsy did not indicate that any patient in group II could have been saved by a more intensive treatment.

Table 8.
Patients Dying of Thromboembolic Complications.

I: 21 in 36 deaths. II: 7 in 20 deaths.

	I	II
Sex — Age		
♀	12 (73) ¹	2 (67) ¹
♂	9 (64)	5
Duration of illness		
> 10 years	7	1
5—10 „	4	2
1—5 „	5	4
< 1 „	5	0
Graduation of decompensation		
I	11	1
II	5	0
III	5	6
Groups of treatment		
I	11	1
III	2	0
IV	3 + 3 ²	2
V	1	0
VI	1	4

Character of complications.

I: Deaths from pulmonary embolism at autopsy: 13
 Deaths from pulmonary embolism without autopsy: 3.
 Deaths from pulmonary infarction: 2.
 Multiple thrombosis found at autopsy: 3².

II: Pulmonary embolism: 7.
 Judged by renal function, fixed arrhythmia, febrile complications:
 The two groups are comparable.

¹ Average age.

In the same period F.H. had 80 survivors, 36 fatal cases (about 30 %); about 14 % died of pulmonary embolism. Table 7 shows the causes of death. The findings at autopsy did not indicate that more intensive therapy could have saved any patient, who died without thromboembolic complications.

Yet in the group of cases described as *large heart with sudden death* the post-mortem examination gave no explanation as to the cause of death.

Table 8 shows how patients who died with thromboembolic complications are distributed over the gravity and treatment groups. They were not exceptionally ill, almost all were treated intensively. In the case notes for 17 of the 21 patients from F.H. who died of or with thromboembolic complications it was repeatedly stated that there was distinct improvement in the condition. Several were completely compensated. The urine output volume of these patients were as in the survivors. For other data, see Table 8.

Patients who died without thromboembolic complications (F.H.), on the other hand, are grouped among the most severely affected. Treatment was fairly intensive, but the patients did not recover, and they died rather quickly. The urine volumes were not large, but often it was impossible to measure them, the patients being very ill and incontinent. For data see Table 9.

Table 9.

Patients Dying Without Thromboembolic Complications.

I: 15 in 36 deaths (surviving: 80).

II: 13 in 20 deaths (surviving: 64).

	I	II
Sex— Age		
♀	7 (76) ¹	6 (63) ¹
♂	8 (68)	7 (68)
Duration of illness		
> 10 years	5	1
5—10 »	2	3
1—5 »	2	8
< 1 »	6	1
Graduation of decompensation		
I	3	3
II	4	5
III	8	5
Group of treatment		
I	5	1
II	3	0
IV	4	2
V	2	7
VI	1	0
VII	0	2

¹ Average age.

Judged by renal function, fixed arrhythmia and febrile complications the two groups are comparable.

Roughly, the same applies to the fatal cases from Sv.C.H. 3 of the patients who died of pulmonary embolism were distinctly improving. The rest were among the most severely affected, not responding to treatment, which in this group was fairly intensive. Table 9.

Conclusions: Patients from F.H. were elderly, several had been ill for many years. Grouped according to the degree of decompensation the patients from the two series were equally affected. 31 % died at F.H., 24 % at Sv.C.H. 14 % (F.H.) and 8 % (Sv.C.H.) died of pulmonary embolism. The difference between the numbers of thromboembolic complications is not so great as in the survivors. A common characteristic of both materials is that the patients dying without fatal thromboembolic complications were as a rule more severely ill. They did not respond to treatment. Many patients dying from pulmonary embolism were not very ill, were improving, or even compensated. They died at a time when they should apparently have been past danger.

Discussion.

It seemed to us in Medical Department E of Frederiksberg Hospital somewhat strange that the number of thromboembolic complications in cases of cardiac decompensation, despite an apparently very effective therapy, tended to increase. In going through the literature, evidence was found showing that the treatment instituted might aggravate a pre-existing tendency to thrombosis in these patients,

either by altering the viscosity of the blood through rapid dehydration, or by a more direct influence of the drug now on the coagulation mechanism.

I have been unable to find any clinical publications recording how frequently thromboembolic complications were found in the different forms of dehydration. A control series is also lacking.

It was natural to look for 2 groups of cardiac decompensation cases subjected to different treatment, one group to the modern rather active therapy, the other to a conservative one, in order to find out whether there were more complications among the actively treated patients. This proved to be the case, the complication percentage being 32, as against 7 among those treated conservatively. Among the survivors the figures are 32 % against 0.

If these figures are authentic the problem is of great interest. Active treatment is used more and more both at the hospitals and by general practitioners. The number of heart patients is increasing.

But are the two groups of cases comparable?

It is difficult to prove that two groups of cases from different parts of the country are comparable. One group consisted of typical town inhabitants, the other of a mixed town and country population. In the first group there were many patients coming from the poorer classes with no possibility of taking special care of themselves. On the other hand, it may be said that the population of Fyn is notorious for its obesity. The patients were a little older in the series from F.H., several had had treatment at home (often inadequate, it is true) and several had previously been admitted to hospital. The complications did not occur preeminently in these patients, so this is hardly decisive. It is possible that the patients from F.H. were kept alive somewhat longer, and had pathologically and anatomically more advanced heart disease than the corresponding patients from Sv.C.H.

The diagnoses of the two series of cases were made by different physicians, whose description of the degree of affection would be coloured by what they were accustomed to see. Different modes of treatment among general practitioners may have some influence on the value of the material.

Despite all these objections it is my impression that patients in the two groups as judged by their degree of decompensation were approximately equally affected, and that the difference in the number of complications was due to the different principles of treatment. This view is in some degree supported by the fact that I have worked for over one year in both departments.

The investigation seems to have answered the question of which element of the therapy it is that aggravates the pre-existing tendency to thrombosis. Intensive treatment with cedilanide and mercurials seems decisive, the amount of the urine volume (or rather the loss of fluid) may be of importance.

Further clinical and experimental investigations are in progress.

Anticoagulation Treatment.

Some recent communications have appeared, describing the favourable effect of a prophylactic anticoagulation treatment of cardiac decompensation cases during

dehydration. Thus Griffith et al. found a reduction of thromboembolic complications from about 30 % to about 10 % in a mixed series of 354 patients (control group 162). The anticoagulation treatment was continued until the stasis had disappeared or the patient could be discharged. These authors state that a fixed arrhythmia, previous cases of decompensation, or thromboembolic accidents do not increase the frequency of the complications (which accords well with the findings in the present material). Further details of therapy are not mentioned.

Harvey and Finch found no undoubted cases of pulmonary embolism in 80 patients treated with dicumarol and 15 cases among 100 not treated. The mortality in the 2 groups during stay in hospital was 9 and 17 %. The patients were only treated with digitalis by mouth. Anderson and Hull out of 147 patients treated with dicumarol found a mortality of 7.5 %, complication percentage 2. Control group: 150 patients. Mortality 13 %, complication percentage 8. No other details of therapy were given. It would be a strenuous task, not quite without risk, to treat all cases of cardiac decompensation with anticoagulants during dehydration. So far no laboratory test has been found that can tell us anything about the patient's tendency to thrombosis, which would make it easier to see the indications for such treatment. In cases where dehydration must be intensive the patients should probably be treated with anticoagulants.

Summary.

The present work proposes to investigate whether a more intensive treatment of cardiac decompensation increases the number of thromboembolic complications.

In rapid diuresis the viscosity of the blood is increased.

Several authors have demonstrated that digitalis and mercurial diuretics tend to shorten the coagulation time.

Either factor may enhance a pre-existing tendency to thrombosis.

Two groups of decompensated patients have been analysed.

I. 116 patients, most of whom had intensive treatment with cedilanide and mercurial diuretics intravenously. 80 survived, 36 (31 %) died. 32 % of the survivors had thromboembolic complications, 15 % a thromboembolic pulmonary complication. Of the 116 patients 14 % had a fatal pulmonary complication.

II. 99 patients, who had very conservative treatment. $\frac{3}{4}$ had digitalis by mouth, $\frac{1}{4}$ had mercurial diuretics intravenously. There were no thromboembolic complications among survivors in this group. Fatal pulmonary complication occurred in 8 %. Overall mortality was 24 %.

Complications seemed to occur particularly in patients who had intensive treatment. The patients with complications generally exhibited the larger urine output, although this relationship is not absolute.

The author is of the opinion that the patients in both groups are comparable. There is no difference as judged by degree of cardiac decompensation. Group I comprises a greater number of elderly patients, patients who had been previously admitted to hospital, and patients who had received treatment at home before admission, but complications show no preference for these categories. Prophylactic treatment with anticoagulants should be contemplated.

References.

- Andersen, W. Thune: Månedsskrift for praktisk lægegering og social medicin, maj, 1942. — Anderson, G. M. and Hull, E.: Am. Heart J., 39: 697, 1950. — Beaumont, Jean-Louis et Lenègre, Jean: La Semaine des Hôpitaux de Paris, No. 49, 2 juillet, 1951. — Bereu, B. A., Rokaw, S. N. and Massie, E.: Circulation, 2: 409, 1950. — De Takats, G., Trump, R. A. and Gilbert, N. C.: J.A.M.A., 125: 840, 1944. — Griffith, G. C., Stragnell, R., Levinson, D. C., Moore, F. J. and Ware, A. G.: Ann. Int. Med., 37: 867, 1952. — Harvey, W. P. and Finch, C. A.: New England J. Med., 242: 208, 1950. — Hines, L. E. and Hunt, J. T.: Ann. Int. Med., 15: 644, 1941. — Judson, W. E.: Med. Clin. North Am., 35: 1333, 1951. — Lowe, T. E.: Lancet, ii: 851, 1951. — Macht, D. J.: Am. Heart J., 31: 460, 1946. — Marvel, R. J. and Shullenberger, W. A.: Am. Heart J., 42: 194, 1951. — Massie, E., Stillerman, H. S., Wright, C. S. and Minnick, V.: Arch. Int. Med., 74: 12, 1944. — Pere, S.: Ann. med. int. Fennicæ, 36: 124, 1947. — Russek, H. J. and Zohman, B. L.: J.A.M.A., 139: 922, 1949. — Seeher, O.: N. M., 35: 1580, 1947. — Wishart, J. H. and Chapman, C. B.: New England J. Med., 239: 701, 1948. — About renal function in cardiac decompensation: Friedberg, C. K.: New England J. Med., 245: 812, 1951. — Elkinton, J. R., Squires, R. D. and Bluemle, L. W. Jr.: Circulation, 5: 58, 1952.
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Adrenal Function and Hyperlipemia in Nephrosis and Diabetic Nephropathy.

By

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(Submitted for publication August 19, 1953.)

The cause of the increase in the serum lipid concentration in certain renal diseases, particularly in nephrosis and some stages of nephritis, has not yet been fully clarified. The mechanism responsible for the »idiopathic» hyperlipemia and for the hyperlipemia in diabetic nephropathy is entirely obscure. *Since there are some grounds for assuming that a change in the function of the adrenal glands affects fat metabolism, we have attempted in the present work to study the adrenal activity in patients with these diseases.*

Hyperfunction of the adrenal cortex (Cushing's syndrome) is accompanied by an abnormal distribution of body fat and a sustained elevation of serum cholesterol and phospholipids. On the other hand, there are apparently rather wide variations in the blood lipid concentration in patients with adrenal insufficiency. Some observers have noted an increase and others a decrease in the serum lipids in this disorder. In 1945 Hoffmeyer demonstrated hypercholesterolemia in rabbits after adrenal homotransplantation, although a corresponding decrease was not obtained following adrenal extirpation. Omura (1930) and Goldzieher (1934) were of the opinion they could demonstrate that adrenal extract »causes fixation of blood lipids in the tissues». In 1936 Verzar and Laszt reported that adrenal extirpation prevented the occurrence of experimentally induced fatty liver or made its provocation more difficult. This observation has since been verified by a number of investigators.

The study of the effect of the administration of ACTH or Cortisone on the serum lipid concentration in individuals without signs of »endocrine» disease has shown it to be variable and, on the whole, inconsiderable. Adlersberg et al. (1951) reported an increase in serum cholesterol after the administration of Cortisone. Perara et al. (1950) found a decrease in serum cholesterol, while Conn et al. (1950) found no concentration change whatsoever. Emerson et al. (1951) studied

the blood lipid concentrations after ACTH administration, also in normal individuals, and found no constant change at all.

The serum lipid concentrations have been studied after administration of ACTH or Cortisone in patients with nephrosis also (Soshea et al., 1951; Lnetscher et al., 1951; Emerson et al., 1951). The results are partially conflicting. They show, however, that no essential change in the serum lipid concentration in nephrotic patients is obtained following administration of these hormones.

In an attempt to estimate the adrenal activity the concentration of Compound F in plasma was determined; in certain cases after the administration of ACTH also. In some cases microchromatographic separation of 17-ketosteroids in urine was also performed.

Methods.

Cholesterol and phospholipids were determined according to methods described in an earlier work (Svanborg 1951). The total lipid concentration was determined gravimetrically after Soxhlet extraction for five hours with absolute alcohol.

The Compound F concentration in plasma was determined according to a method reported by Nelson et al. (1951): The plasma was extracted with chloroform. The chloroform extract was evaporated and the residue separated chromatographically on a column of Celite-magnesium silicate. On the fraction containing Compound F a colorimetric reaction was subsequently obtained with phenylhydrazine, which has been proved to be a specific reagent for steroids with a side-chain of dihydroxy-acetone type (Porter and Silber, 1950).

The adrenal function was tested by the administration of 25 mg of ACTH intramuscularly. Compound F was determined in the plasma before and two and four hours after the injection. Normally, this procedure induces a two- to four-fold increase in the Compound F concentration in the blood.

Microchromatographic separation of the 17-ketosteroids was done according to Zygmuntowicz et al. (1951).

Material.

The five nephrosis patients examined all had a classic lipid nephrotic syndrome with massive albuminuria, hyperlipemia, hypoproteinemia with a typical electrophoretic diagram, and periodic edema. Concurrently, one of them (T.L.) had a slight rise in non-protein nitrogen. Four cases of diabetic nephropathy were studied. See table.

Conclusions.

The Compound F concentration in plasma in all cases examined fell within the normal limits. In two of the nephrosis cases, however, values were demonstrated at the lower limit of the normal. In three nephrosis patients the ACTH test was also performed: *i. e.* the Compound F concentration was determined before and after the administration of 25 mg of ACTH. In the two nephrosis cases in which

Table.

Patient	Diagnosis	Cholesterol mg/100 ml serum	Lipid phosphorus mg/100 ml serum	Total lipids mg/100 ml serum	Compound F γ /100 ml plasma
L. M.	Nephrosis	830	19	2,100	7.2 10.7 2.4—6.8 ¹
W. E.	»	480	16	1,600	25.6 31.0 4.2
S. B.	»	660	14	2,100	5.3 2.1—4.3 ¹
G. B.	»	500	15	1,600	10.5 9.5—22.0 ¹
T. L.	» (Nephritis chron.?)	380	12	1,300	12.9
B. H.	Diabetic Nephropathia	390	12	1,600	13.0
G. S.	»	370	9	1,700	8.0
S. C.	»	480	8	1,500	11.5
A. S.	»	540		2,100	11.3 12.3

¹ ACTH-test.

low Compound F concentrations were shown before the administration of ACTH, a poor adrenal response was obtained. In the third nephrosis patient examined, however, there was a normal rise in the Compound F concentration after ACTH administration.

Fractionation of the 17-ketosteroids in the urine of two of the nephrosis patients with grave hyperlipemia showed a normal distribution. In one of these patients, however, the total quantity of 17-ketosteroids excreted was low (1.8 mg per 24 hours). This investigation has not yet been completed. The results will be reported later.

Bilateral nephrectomy or ligation of the ureters is accompanied by a hyperlipemia of the same qualitative composition and of the same order of magnitude as that in nephrosis. (A review of the literature in this field has been published earlier, Svanborg, 1951.) Accordingly the Compound F concentration in serum was determined in a dog before and after bilateral ligation of the ureters with concomitant hyperlipemia. No change in the Compound F concentration was demonstrated.

The plasma concentration of steroids with a side-chain of dihydroxy-acetone type may, in all probability, be regarded as an indicator of the adrenal activity. For this reason determination of the concentration of such steroids (Compound F) was selected for the present study. In all cases examined it lay within the normal limits.

It seems reasonable to assume that if a disturbance in the adrenal activity were the cause of a hyperlipemia of the magnitude encountered in this investigation, there should be an extensive change in the adrenal activity. In Cushing's syndrome, however, in comparison to nephrosis-hyperlipemia, the rise in the blood lipids is inconsiderable.

Accordingly, this investigation gives no support to the theory that the hyperlipemia in nephrosis and diabetic nephropathy might be based upon impaired adrenal activity. However, since our knowledge of the manner in which the steroid balance in the blood is maintained is still imperfect clearly no definite conclusions can be drawn.

Summary.

Because certain observations indicate that disturbances of the adrenal activity may affect lipid metabolism, an attempt was made to estimate the adrenal activity in five cases of nephrosis with grave hyperlipemia, in four cases of diabetic nephropathy, and in one dog with hyperlipemia following bilateral ligation of the ureters.

The Compound F concentration in all cases lay within normal limits.

Fractionation of urinary 17-ketosteroids in two cases of nephrosis showed a normal percentual steroid composition.

In three of the cases of nephrosis the Compound F concentration was determined both before and after administration of ACTH. In two of the cases of nephrosis a poor adrenal response was obtained, such as is seen in some patients with severe, chronic diseases. In no case were results obtained that might indicate increased adrenal activity.

Consequently, this investigation gives no support to the theory that the cause of the hyperlipemia in the diseases studied might be impaired adrenal activity.

Bibliography.

- Adlersberg, D., Drachman, S. R., Schaeffer, L. E., Dritch, R.: *J. Clin. Investigation* 1951, 30, 626. — Conn, J. W., Vogel, W. C., Lawrence, B. S., Louis, H., Fajans, S. S.: *J. Lab. & Clin. Med.* 1950, 35, 504. — Emerson, K. Jr., Roche, M., Kahn, S. S., Moser, H. V., Jenkins, D.: *J. Clin. Investigation* 1951, 30, 637. — Goldzieher, M. A.: *Endocrinology* 1934, 18, 179. — Hoffmeyer, J.: *Acta physiol. Scandinav.* 1945, 10, 31. — Luetseher, J. A. Jr., Deming, Q. B., Johnson, B. B.: *J. Clin. Investigation* 1951, 30, 658. — Nelson, D. H., Samuels, L. T., Willardson, D. G., Tyler, F. H.: *J. Clin. Endocrinology* 1951, 11, 1021. — Omura: *Folia endocrin. Japon* 1950, 5, 119. — Perara, G. A., Fleming, T. C., Pines, K. L., Crymble, M.: *J. Clin. Investigation* 1950, 29, 739. — Porter, C. C., Silber, R. H.: *J. Biol. Chem.* 1950, 185, 201. — Soshea, J. W., Farnsworth, E. B.: *Proc. 2nd Clin. ACTH Conf.* 1951, 1, 318. — Svanborg, A.: *Acta med. Scandinav.* 1951, 141, suppl. 264. — Verzar, J., Laszt, L.: *Biochem. Zschr.* 1936, 288, 351. — Zygmuntowicz, A. F., Wood, M., Christo, E., Talbot, N. B.: *J. Clin. Endocrinology* 1951, 2, 578.

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Anomalous Drainage of Pulmonary Veins from the Right Lung to the Superior Vena Cava with Patent Foramen Ovale, as the Cause of Congestive Heart Failure in a 68-year-old Man.

By

OLE STORSTEIN and HANS TVETEN.

(Submitted for publication July 7, 1953.)

Anomalous drainage of pulmonary veins, which in Abbott's series of 1,000 congenital anomalies of the heart and great vessels was reported in 58 cases (in only 4 of which did it constitute the primary lesion), is now frequently found, on cardiac catheterisation, in patients with congenital cardio-vascular anomalies. Cosby and associates, in catheterisation studies of 145 such patients, observed transposed pulmonary veins from the right lung in 11 cases. Friedlich and associates reported that among 34 cases of anomalous venous return they found 18 cases of transposed pulmonary veins. According to White this diagnosis had not previously been made in vivo. Several authors have, however, been able to diagnose pulmonary veins draining into the inferior vena cava by means of ordinary X-rays of the chest, in that they find a characteristic falciform shadow in the right lower lung field (Dotter and associates; Walti and Nedey; Snellen and Albers).

The anomaly is most frequently found on the right side, but it may also occur from both lungs. The anomalous veins drain most frequently into the superior vena cava or the right auricle, but they may also enter the innominate vein, the inferior vena cava, the azygos vein or the coronary sinus.

Anomalous drainage of a single pulmonary vein is of little importance, whilst complete transposition of all the pulmonary veins to the right heart is a grave anomaly, usually resulting in death in infancy. The life of these individuals is dependent upon the patency of the foramen ovale. The left auricle is small and rudimentary, and there is a strong tendency to closure of the foramen ovale.

Among 106 cases of abnormal drainage of the pulmonary veins in Brody's series, 38 were complete. Of these only 8 lived for more than six months. Taussig reports 3 subjects who died at ages varying between $3\frac{1}{2}$ months and 4 years; Friedlich and associates report 2 subjects who died at ages of 2 and 4 years respectively.

Kera has observed the survival to the age of 27 of a patient with complete drainage of the pulmonary veins to the right auricle. Snellen and Albers report 4 cases of drainage of all the pulmonary veins into the superior vena cava. The patients were respectively 5, 7, 20 and 22 years old.

When 2 or more pulmonary veins drain into the right heart the ensuing left to right shunt will be of the same importance as a patent ductus arteriosus or an auricular- or ventricular-septal defect.

We have recently, in the case of a 68-year-old man, observed such an anomaly, which gave rise to grave congestive heart failure.

The patient, R. E., was born on March 3rd, 1885. He had been employed as a construction worker up to 1948, when he had to give up his work on account of dyspnoea, which became progressively worse, until from 1950 onwards he had nocturnal dyspnoea accompanied by paroxysmal tachycardia and non-irradiating pains in the left side of the chest which lasted for half an hour at a time.

During 1952 he had some swelling of the ankles, which increased progressively up to his admission to hospital on December 5th, 1952.

He was found to have slight cyanosis of the face, hands and feet, dependent oedema in the back and feet, and kyphosis with increased anterior-posterior chest diameter and precordial bulging. The blood-pressure fell from 160/110 to 120/70 during his stay in hospital. The pulse rate was 80, irregular. The liver was 6 cm below the costal margin. The point of maximum impulse was found 11 cm from the midline in the 5th intercostal space, in the anterior axillary line. At the apex the first sound was snapping, and there was a systolic murmur grade 2 to 3 and a short, rumbling diastolic murmur. P2 was accentuated. The heart action was irregular, $C = P = 80$. The eye-ground was normal. Height 159 cm. Weight 68 kg.

The proteinuria found on admission soon disappeared. MKR II reaction was negative. Hg/b. 11.1 g/100 ml. Red blood corp. 4.14 mill. White blood corp. 6,700. The differential count was normal. Sedimentation rate 4 mm/1 hour. Blood urea 43 mg/100 ml. Thymol turbidity 5.3 MacLagan units. X-ray of the heart showed a pronounced enlargement of the right ventricle, right auricle and pulmonary conus, with increased pulsations of the pulmonary vessels. The roentgenological heart volume was 1,700 ml, *i. e.* 1,000 ml/m² body surface. (Plate 1, fig. 1.) The electrocardiogram showed auricular fibrillation and right ventricular strain (fig. 2).

His treatment consisted of rest in bed, a diet poor in salt, and theophyllamine, digitalis and mercurial diuretics. His auricular fibrillation was regularized with quinidine, and he was treated with dieumarol to prevent embolism. When he left the hospital, on January 14th, 1953, he was ambulatory and without oedema, but he still had dyspnoea on exertion. The weight was 56.2 kg.

Physiological Studies.

Venous pressure 20 mm. Circulation time, arm to tongue (deeholin) 16 seconds for the first taste, 28 seconds for the last. The findings on heart catheterisation are shown in table 1 and the ventilatory performance in table 2. The successive positions of the cardiac catheter are shown in figs. 3—5 (Plate 1).

Table 1.

Results of right heart catheterisation.

Catheter location	O ₂ Content (Vol.%)	Pressures mm Hg syst./diast.-mean
Superior vena cava	10.09	8.5/0.5 — 3
Anomalous pulmonary vein I (fig. 3)	15.35	11.5/2 — 4.5
Anomalous pulmonary vein II (occluded) (fig. 4)	12.97	15/9 — 10
Right auricle	13.33	8/0 — 2
Inferior vena cava	11.46	7.5/—1 — 0.5
Right ventricle	—	53/—2
Pulmonary artery (fig. 5)	12.54	59/18 — 26

Arterial oxygen content 14.23 Vol.% Art. CO.-content 66.07 vol.%

Oxygen capacity 17.17 » Pulm. vein » 65.36 »

Arterial oxygen saturation 83.— %

Oxygen saturation of pulmonary venous blood 89.6 %

Oxygen consumption 242.6 ml/min.

Cardiac output:

systemic flow 7.0 litres/min. C. I. 4.5 lit/min/m².

pulmonary artery flow 8.6 litres/min.

effective pulmonary flow 5.3 litres/min.

total shunt left to right 3.3 litres/min. (38 %)

interauricular shunt right to left 1.7 litres/min. (24 %)

Pulmonary arteriolar resistance 215 dynes sec./cm⁻⁵.

Work of right ventricle 2.34 kgm/min.

Table 2.

Ventilatory function studies.

Vital capacity	1,700 ml.
Residual air	2,700 »
Total capacity	4,400 »
$\frac{RA}{TC} \times 100$	61 %
Maximum breathing capacity	13.2 litres.

Discussion.

The clinical findings in this patient, with the snapping first heart sound and the short, rumbling diastolic murmur at the apex, point towards mitral stenosis. The suspicion of mitral stenosis is often aroused in cases of left to right shunt, as in patent ductus arteriosus. The low-pitched murmur at the apex is here assumed to be caused by the rapid filling of the left ventricle due to the increased blood supply returning from the lungs (Levine and Geremia).

The demonstration, on cardiac catheterisation, of a left to right shunt amounting to 38 per cent of the pulmonary artery flow, fits in with the observation of an abnormal venous return of two-fifths of the lung veins.

Pulmonary function studies in this patient reveal a reduced ventilatory performance. The alveolo-respiratory function is also reduced with regard both to

oxygen saturation and to carbon dioxide elimination. The demonstration of a greater reduction of the oxygen saturation in the arterial blood than in pulmonary venous blood is, in all probability due to a persistent foramen ovale. The calculation reveals a right to left shunt of 24 per cent of the systemic blood flow from the right to the left auricle.

The pressures registered by occlusion of the pulmonary vein (Plate 1, fig. 6) show the characteristics of pressures in this position: they resemble the pressures in the pulmonary artery, they are higher than the pressure in the non-occluded pulmonary vein, and there is a time-lag between the onset of the rise in the systolic pressure in the pulmonary artery and that in the occluded pulmonary vein (Weissel and associates). The oxygen content of the blood aspirated in this position is the same as that in the pulmonary artery (table 1), so that we may call this blood, »pulmonary capillary artery blood», and the pressure »pulmonary capillary artery pressure».

The existence of a shunt of this magnitude will mean an increased load on the circulation. It is, however, compatible with the leading of an active life over a period of many years. Dean and Fox mentioned a patient who lived for 86 years with drainage of the pulmonary veins from the left lung to the innominate vein. Gérard and Leroy observed the survival to 71 years and Gérard to 70 years of subjects with this anomaly. We have previously published the case-history of a 72-year-old woman with a shunt of 52 per cent, who was still attending to her household duties (Storstein and associates).

The burden of the increased blood flow through the pulmonary circulation will be placed on the right ventricle and the pulmonary arteries. The pulmonary blood flow must be increased to 3 times the normal before the appearance of a pressure rise in the pulmonary artery (Cournand). This, however, refers to acute exercise tests. We must presume that the existence of a shunt of this magnitude over a period of more than 60 years will provoke pulmonary arterial hypertension. Susceptibility of the pulmonary vessels to pathological stimuli seems to be an individual matter, as shown by Wood, who found that about 20 per cent of patients with left to right shunt (auricular- or ventricular-septal defects or patent ductus arteriosus) showed increased pressures in the pulmonary circulation, irrespective of the duration of the shunt.

The increased pulmonary resistance in this patient (215 as against the normal 74.8 ± 12.8 dynes/sec/cm⁻², Storstein) will mean an increased load on the right ventricle, whose work is thus increased to about 3 times the normal average (2.34, as against the normal 0.75 ± 0.48 kgm/min. Storstein). This explains why it is that the right ventricle fails, with resulting congestion of the systemic circulation. The cardiac output of the systemic circulation is normal in this patient, which points to a »back pressure»-effect rather than to a »forward failure».

The treatment of this patient is directed towards his congestive heart failure. In younger age-groups with this anomaly it is now possible to treat the malformation surgically, as has been done by Muller, who in one case has successfully transplanted anomalous left pulmonary veins to the left auricle.

Summary.

Congestive heart failure in a man aged 68 is shown by cardiac catheterisation to be the result of anomalous drainage of 2 pulmonary veins to the superior vena cava. The finding of greater reduction in the arterial oxygen saturation than in that of pulmonary venous blood points towards the persistence of a patent foramen ovale.

The pulmonary arterial hypertension in this patient is believed to be caused by the increased blood flow through the pulmonary vessels, which places an increased burden on the lesser circulation.

Only 3 patients with longer longevity have been reported in this condition. In younger age-groups this anomaly may be corrected surgically.

Literature.

1. Abbott, M. E.: Atlas of congenital heart disease. New York 1936. — 2. Brody, H.: Arch. Path. 1942: 33: 221. — 3. Cosby, R. S., Griffith, G. C., Levinson, D. C., Oblath, R. W., Zinn, W. J., Dimitroff, S. P., Herman, L. M. and Reynolds, T. B.: Med. Clin. North. Am. 1952: 1035. — 4. Cournand, A.: Circulation 1950: 2: 651. — 5. Dean and Fox, cit. Brody. — 6. Dotter, C. T., Hardisty, N. M. and Steinberg, I.: Am. J. Med. Sc. 1949: 218: 31. — 7. Friedlich, A., Bing, R. J. and Blount, S. G.: Bull. Johns Hopkins Hosp. 1950: 86: 20. — 8. Gérard, cit. Brody. — 9. Gérard and Leroy, cit. Brody. — 10. Kera, cit. Brody. — 11. Levine, S. A. and Geremia, A. E.: Am. J. Med. Sc. 1947: 213: 385. — 12. Muller, W. H.: Ann. Surg. 1951: 134: 683. — 13. Snellen, H. A. and Albers, F. H.: Circulation 1952: 6: 801. — 14. Storstein, O.: Acta Med. Scandinav. 1952, suppl. 269. — 15. Storstein, O., Hummerfelt, S., Müller, O. and Rasmussen, H.: Brit. Heart J. 1952: 14: 276. — 16. Taussig, H. B.: Congenital malformations of the heart. New York 1947. — 17. Walti, J. J. and Nedey, R.: Arch. de Mal. du Cœur 1950: 43: 464. — 18. Weissel, W., Salzmann, F. and Vetter, H.: Brit. Heart J. 1952: 14: 47. — 19. White, P. D.: Heart Disease. New York 1947. — 20. Wood, P.: Brit. Med. Bull. 1952: 8: 348.
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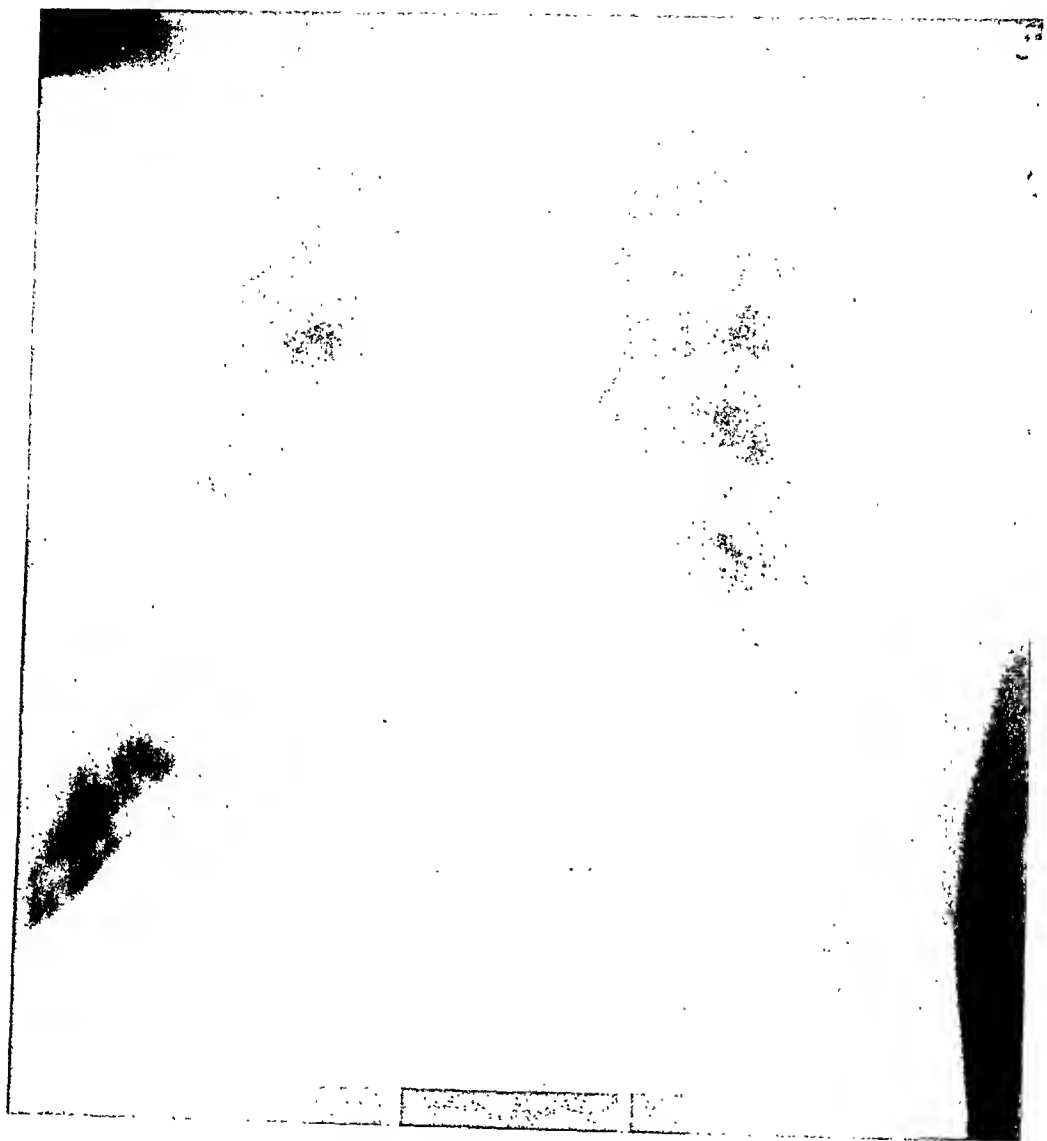


Fig. 1. Teleradiogram of the heart.

STORSTEIN and TVETEN: Anomalous Drainage of Pulmonary Veins.

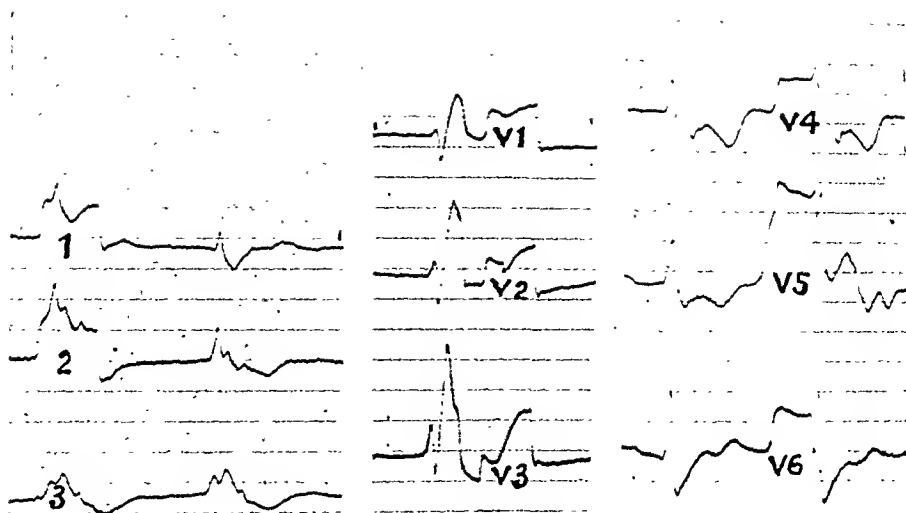


Fig. 2. Electrocardiogram.



Fig. 3. Catheter in anomalous pulmonary vein I.

STORSTEIN and TVETEN: Anomalous Drainage of Pulmonary Veins.

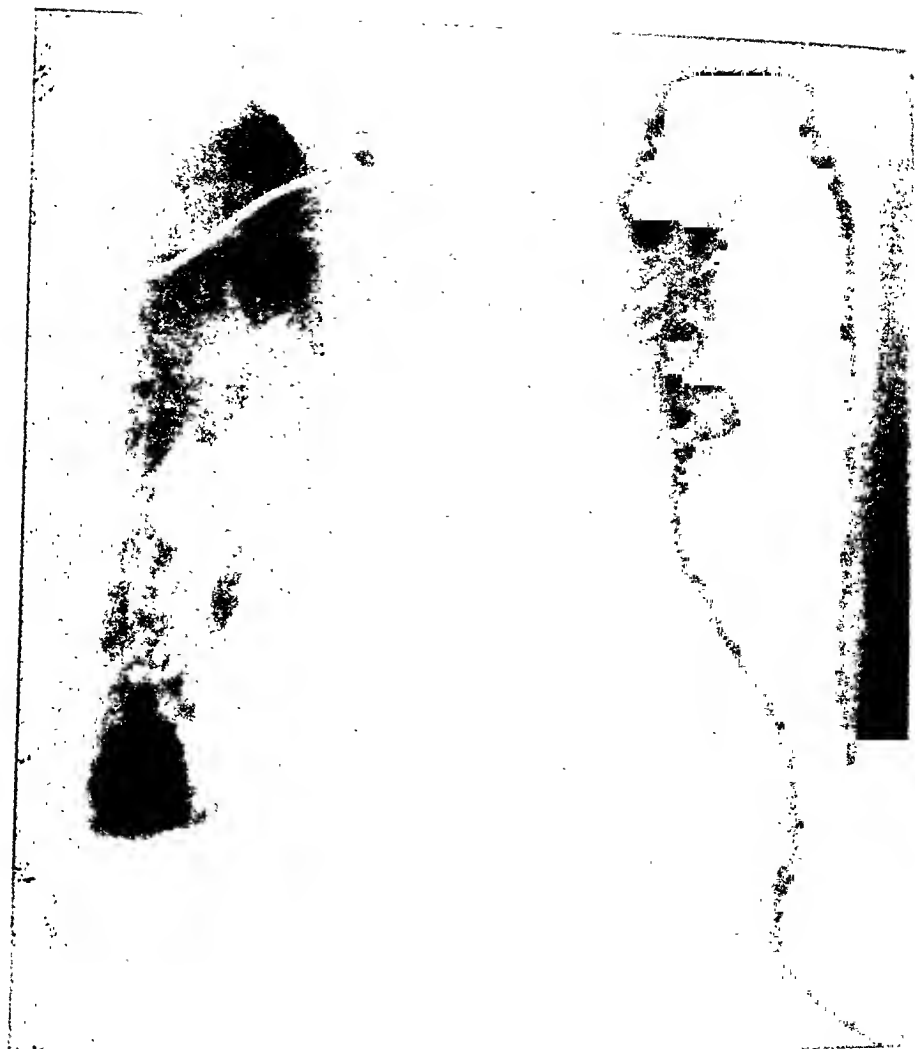


Fig. 4. Catheter in anomalous pulmonary vein II.

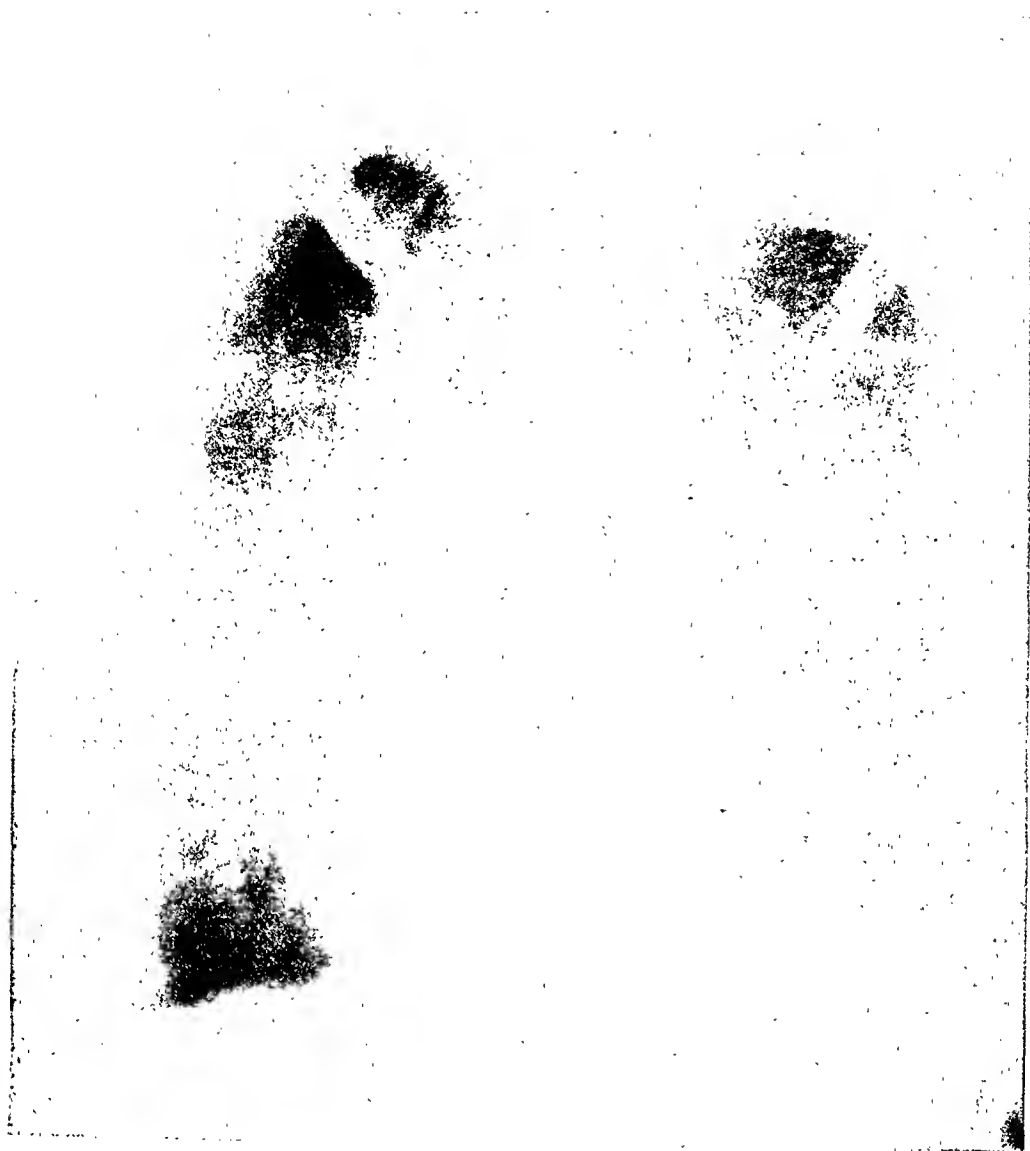


Fig. 5. Catheter in right pulmonary artery.

STORSTEIN and TVETEN: Anomalous Drainage of Pulmonary Veins.

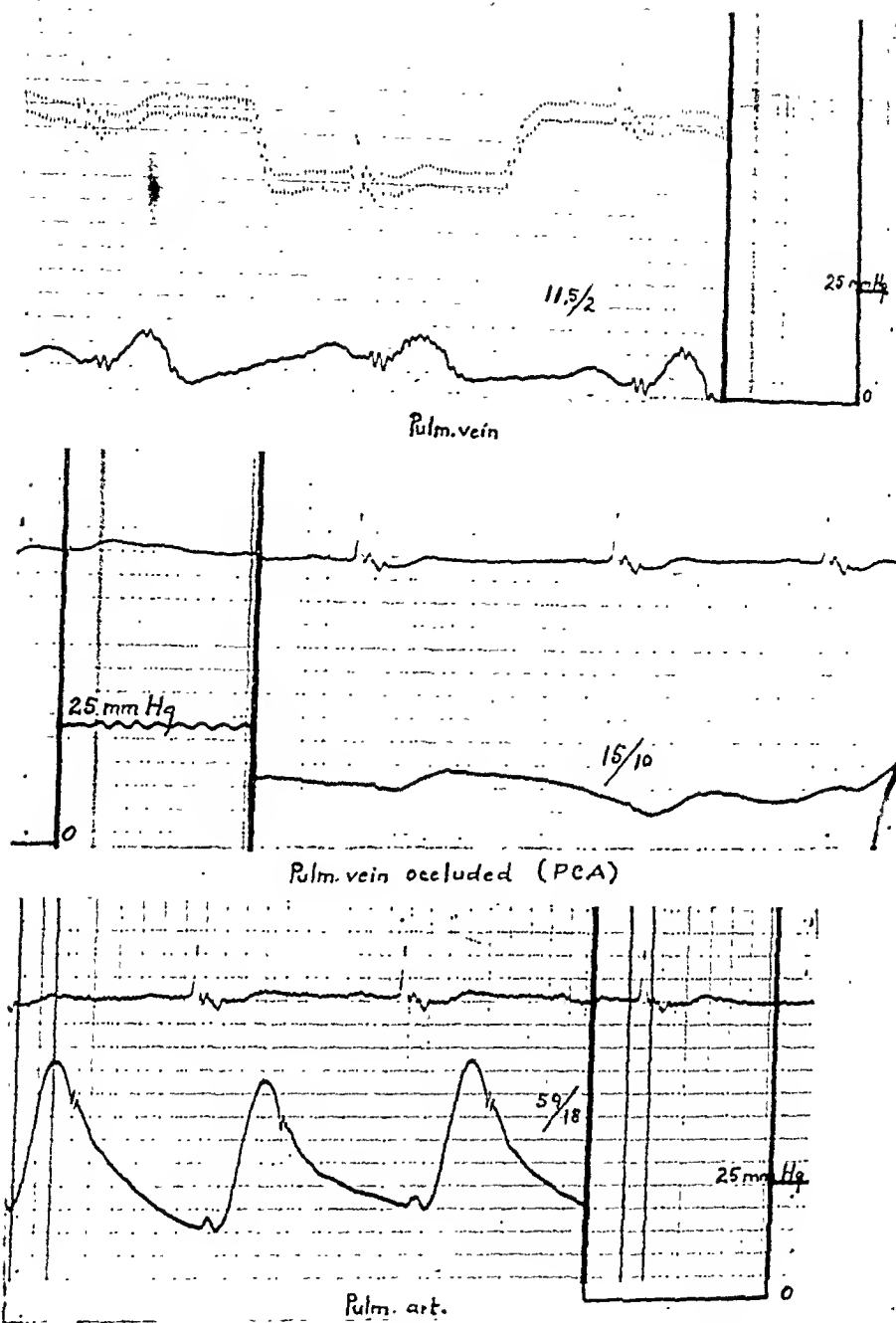


Fig. 6. Pressure recordings from pulmonary vein I, pulmonary vein II (occluded) and pulmonary artery. All pressures undamped.

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New Line of Treatment in Barbiturate Poisoning.

By

CARL CLEMMESSEN.

(Submitted for publication July 16, 1953.)

For years the incidence of suicide has been high in Denmark compared with other countries.

During recent years, the most popular method has been poisoning, particularly where females are concerned.

The introduction of new therapeutic principles (Fig. 1) has reduced the mortality from barbiturate and morphine poisoning treated in hospital from about 25 % to 3.7 %, even down to 1.6 % in Copenhagen, in the course of 6 years. It therefore appears justified to call attention to the therapeutic advances.

As is apparent from Fig. 1 a and b the number of barbiturate and morphine poisonings treated in Danish hospitals has more than doubled (from 1,500 to 3,000) during the period 1945 to 1951, while, at the same time, the mortality has dropped from 24.8 % in 1946 to 3.7 % in 1951. From 1948, Copenhagen and suburbs may be distinguished statistically from the remaining parts of Denmark. It will be seen that in the capital, where the treatment has been centralized in one department (Bispebjerg Hospital, Department of Psychiatry), the mortality has been reduced to 1.6 %. It is the experience from this department which will be presented below.

Historical.

The treatment has been altered through the following stages:

In 1942 gastric washing was abandoned after the studies of Harstad, Møller & Simesen were published.

In 1946, antishock-therapy was introduced after the animal experiments of Aa. Kirkegaard in collaboration with Georg Constantin Brun had shown that following allypropymal (alurate) poisoning, the experimental animals died from shock.

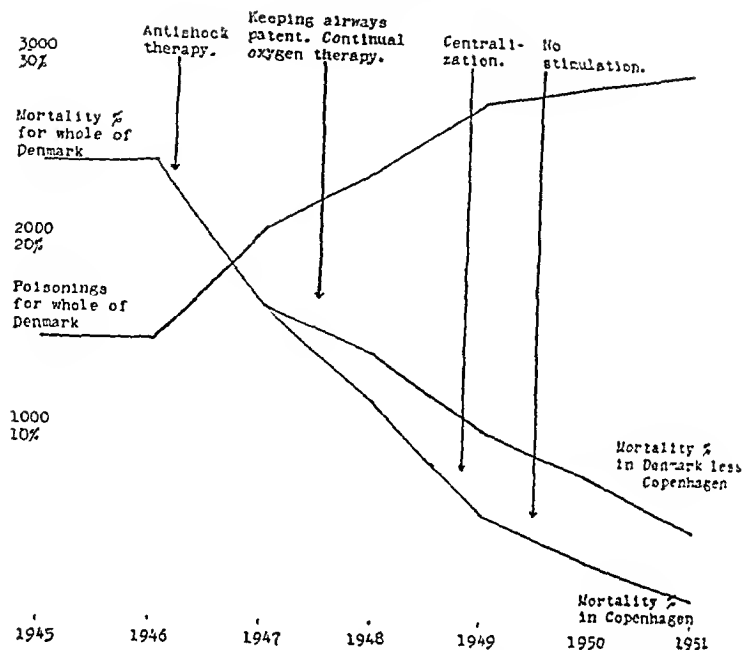


Fig 1. Graphic representation of the values from table.
Mortality as per cent of cases admitted.

Table.

Poisoning with barbiturates, morphine, etc. treated in Danish hospitals 1945—1951.

	Copenhagen		Other parts of Denmark		Denmark as a whole		Mortality as per cent of cases admitted		
	Total cases	Deaths	Total cases	Deaths	Total cases	Deaths	Copen- hagen	Other parts of Denmark	Den- mark as a whole
1945.....		134		235	1,509	369			24.5
1946.....		121		248	1,488	369			24.8
1947.....		122		234	2,122	356			16.5
1948.....	802	96	1,612	234	2,414	330	12.0	14.5	13.7
1949.....	1,041	63	1,749	180	2,790	243	6.1	10.3	8.7
1950.....	1,288	48	1,637	135	2,925	183	3.7	8.2	6.3
1951.....	1,276	21	1,725	90	3,001	111	1.6	5.2	3.7

In 1947, continuous oxygen therapy was introduced with special emphasis on keeping the air passages clear (Lous, Hertel Wulff, Georg, Trier Mørch & Sonne).

In 1949, the treatment of severe poisonings in Copenhagen and suburbs (population 1,200,000) was centralized in one department. About the same time, stimulation was abandoned. On the basis of clinical observations, stimulation had gradually been reduced to a minimum in the hope of avoiding the frequently fatal hyperther-

mia which it induced. Then, in 1951, Eric Nilsson's thesis afforded the theoretical justification for abandoning any form of stimulation.

Organization of the Section for Poisonings.

Patients from Copenhagen with narcotic poisoning are accommodated in a section of the Psychiatric Department of the Bispebjerg Hospital. This section has 4 rooms with a total of 9 beds. At each bed, there are facilities for oxygen administration and suction.

The treatment is carried out by the psychiatrists with the collaboration of anaesthetists, interns, and other specialists. Three nurses are always on duty at the same time, each watch being 8 hours.

The section receives only patients with poisonings so severe as to cause unconsciousness or a risk thereof.

During the past few years, the annual number of patients has been about 800. The average daily number of patients is about 6.6, and the average stay in hospital 3 days.

Therapy.

The *therapy* which has gradually been developed in this centre for the treatment of poisonings, and which has given the results to be reported, is as follows.

From admission until the patient is fully awake and in good general condition, the temperature, pulse rate, and respiration are controlled every other hour and the blood pressure and haemoglobin content every 4 hours. The general condition is watched. Determination of plasma chlorides, plasma bicarbonate, blood urea, serum protein, barbiturate content and, if required, potassium content in the blood are carried out once every 24 hours. Moreover, the daily output and the specific gravity of the urine are controlled as far as possible.

All these values are recorded, with the therapeutic data, on a scheme (Fig. 2) which facilitates the survey of the condition and therapy.

Fig. 2 illustrates a typical course of a severe poisoning treated as described.

A female, aged 22, suffering from epilepsy.

Shortly before admission, the patient had taken about 8.5 g of phenobarbital plus about 8.5 g of phenantoin.

On admission, in deep coma, with areflexia and a blood pressure of 90/60.

For 12 hours in severe shock with a blood pressure decreasing to 80/60, but improved on intravenous administration of a total of 2.5 litres (macrodex (a 6 % solution of dextran), + a solution of dried blood serum + blood + concentrated dry serum).

For 132 hours continuous oxygen therapy, through an endotracheal tube for 48 hours.

On the 3rd, 5th, and 6th days initial shock with haemoconcentration and a falling blood pressure, immediately improved upon intravenous injections.

The barbiturate content of the blood remained strikingly constant and increased (about 17 mg %) for 4 days after which it fell. After 8 days it was still 8.4 mg %.

The temperature, which at the outset had been somewhat subnormal, if anything, ranged from 38° to 39° C, and during the 24 hours before she awoke from 39° to 40° C.

After having stayed in the department for 128 hours, the patient woke up.

B. B. H., Dept. E.

Fig. II.

POISONING SCHEMA.

Remarks

Date 7-7-32. Hour 7:30 p.m.

Name K.S.L.

Case rec. 2213/32 Age 22 Weight 65 kg Usual hypnotic:

Drug: phenobarbital 4 pheneturion Amount 8.5 g mg. per kg. Hours before adm.: ab. t

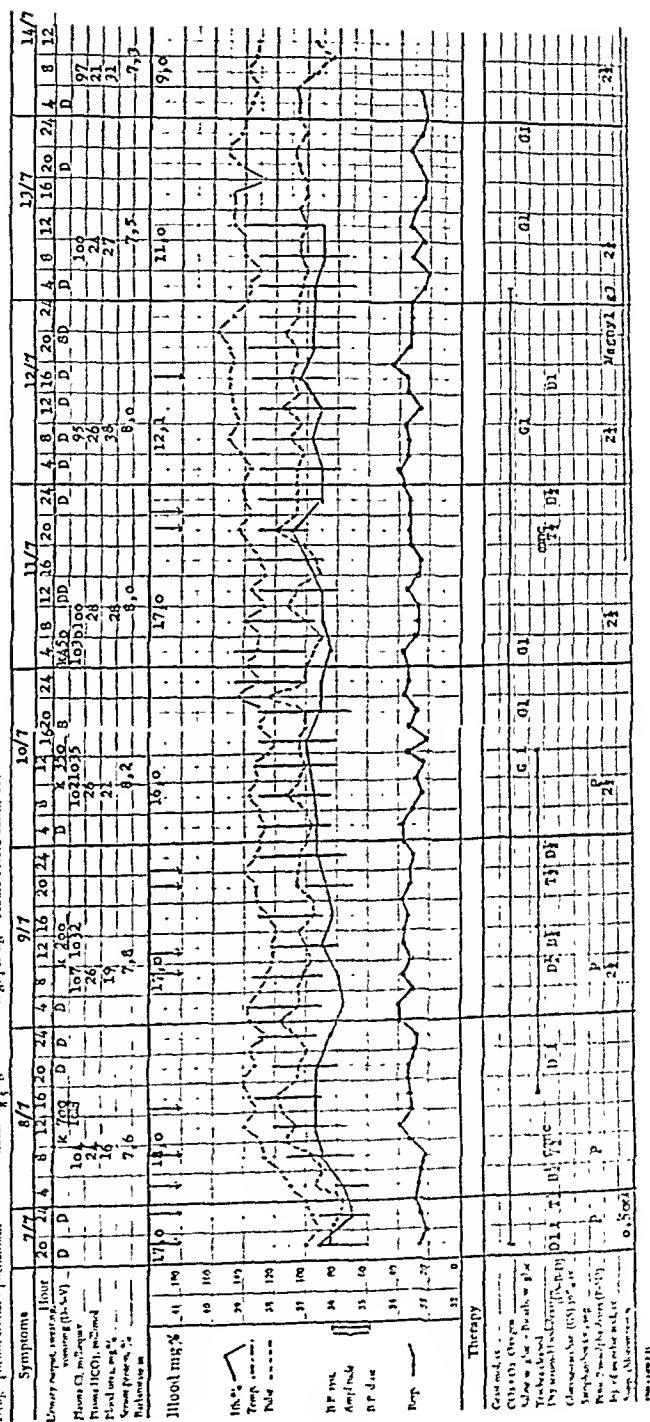


Fig. 2.

The patient is placed in a slight Trendelenburg position during the first few days to prevent aspiration of gastric contents. Heels and knees are packed with cotton wool to prevent decubitus ulcers.

A hollow tongue depressor is inserted through which oxygen is administered continuously.

Every other hour, the patients are turned over. At the same time, intensive slapping of the chest wall and suction of secretion from the air passages are performed.

Procaine penicillin, 300,000 units, is injected subcutaneously every day as a prophylactic measure.

The fluid balance is maintained by subcutaneous or intravenous administration of usually 2 litres of fluid daily.

If *complications* occur, they are immediately treated. *Shock* is often present on admission or may occur during the course of a severe poisoning. The signs of well-marked shock are a poor general condition, rapid pulse rate and respirations, cool extremities, hæmoconcentration, a decreasing blood pressure with a small amplitude. A shock must, however, be arrested before it has become well-marked. Therefore, an alteration in only one respect, such as a fall in blood pressure, may indicate therapeutic measures, *e. g.* blood transfusion or infusion of macrodex or perhaps a solution of dried blood serum. Often $\frac{1}{2}$ litre is sufficient, but in severe cases, 2 or even 3 litres may be required, although care must be taken to avoid pulmonary oedema. Concentrated dry serum, *i. e.* 2 parts of dry serum shaken with one part of fluid, is particularly effective; it is indicated in cases of threatening pulmonary oedema or if there are other reasons for hesitating before administering large amounts of fluid.

Some patients are apt to have shock on almost every day of the poisoning, while others are stabilized after the first 12 or 24 hours in the department.

The *air passages* commonly become obstructed in unconscious patients, resulting in a laboured respiration and at times tachypnoea, fever, and cyanosis. Signs of respiratory obstruction call for suction from the pharynx, tracheal toilet, and, if required, intubation. The tracheal tube must be changed daily, and should not be left for more than 24 or 48 hours, unless absolutely necessary. Signs of atelectasis or other pulmonary complications call for bronchoscopic examination. At an early stage, sensitivity determinations of organisms cultured from the bronchial secretion must be done to decide the most effective antibiotic therapy.

Respiratory paresis, sometimes total apnoea, is common in severe morphine poisoning. The treatment is immediate artificial respiration with a «to and fro aggregate». When performed correctly, artificial respiration can nearly always tide the patients over this crisis, even in severe cases. In 1951, all our 29 cases of morphine poisoning were cured, although 10 required artificial respiration for periods ranging from 3 to 17 hours.

Apnoea may also occur in very severe barbiturate poisonings, but usually at a later stage than in morphine poisoning. The prognosis is much poorer than in the latter.

In the ordinary course of events, any form of *stimulation* has been abandoned.

In respiratory paresis, however, moderate stimulation with geastimol (phthalic-acid-bis-diethylamide) or amphetamine may be indicated, but it is very seldom effective in severe cases. On the other hand, *e. g.* amphetamine, 25 mg intramuscularly, may be helpful in producing a more ample flow of blood in collapsed veins. This facilitates the venous puncture in a patient in shock. Picrotoxin is never used.

Heart failure is rare in the absence of pre-existing heart disease, but not uncommon in cardiac patients with barbiturate poisoning. In that case, strophanthin or cedilanid may be administered and some caution must be exercised in administering fluids.

Gradually as oxygen therapy has become more systematic and effective, *pulmonary oedema* has been reduced to an uncommon complication. Its occurrence indicates intubation with suction and simultaneous intravenous injection of a hypertonic solution of glucose (*e. g.* 100 ml 50 %) and in some cases concentrated dry serum. As a rule, pulmonary oedema rapidly yields to these measures.

Laryngeal oedema may occur in rare cases in which prolonged intubation has been required. It may, in exceptional cases, necessitate tracheotomy, if the patient is unable to breathe without the tube after awakening.

Hypothermia is commonly met with in poisoned patients on admission, if they have been lying out of doors or uncovered in bed. It is important to re-establish the normal body temperature as soon as possible. This is obtained most effectively by placing the patient in one of the arches with incandescent lamps as used in physical therapy. The patient is covered with a sheet and the incandescent arch with blankets so that the heat is distributed all over the body, up to the axillae. By this procedure, it is possible to raise the temperature to normal within a few hours, even though it has shown minimal values on admission.

Hyperthermia was previously a common and dreaded complication, occurring without warning, without demonstrable cause, and, reaching maximum values, not infrequently leading to death.

After stimulation was totally abandoned, these alarming elevations of temperature have practically ceased to occur. If a tendency to fever is observed, it can usually be controlled. Primarily, the cause of the fever must of course be traced, if possible, and treated. In this connection, special attention must be given to the possibility of atelectasis. In some cases, it may be advisable to alternate the antibiotic agents. The immediate regulation of the heat also merits attention. Removal of blankets, leaving the patient with only a sheet over him, is often effective in counteracting fever in coma. In rare cases cold packings may be used or salicylic acid, 3 g, may be administered by rectum. It is important, however, to start treatment *e. g.* at 39° or 39.5° C and not wait until the fever has reached excessive heights.

Course.

In this treatment, it is endeavoured to maintain physiological conditions as far as at all possible during the period of unconsciousness — which in severe poisonings may last for more than 10 days. Even after awakening, the patient must be kept

under painstaking supervision for a few days because, owing to his debilitated condition, he is an easy prey to pneumonia or possibly renal damage.

As stated in the introduction, this line of treatment has proved extremely effective. It has reduced the mortality from narcotic poisoning to a minimum. By now, most of the patients who die are already frail, *e. g.* because of serious heart disease. At the same time, the therapy is gentle and well tolerated as is apparent from the fact that 12 of the severe barbiturate poisonings treated during 1951 involved persons ranging in age from 70 to 85 years (period of unconsciousness from 24 to 144 hours), all of whom recovered.

Summary.

From 1949 the treatment of poisoning in Copenhagen and suburbs has been centralized in one department where about 800 cases are treated annually.

The organization of this department is outlined, the principles of treatment described, and the results reported.

The previously very high mortality has been reduced to a minimum.

References.

Harstad, Elisabeth, Knud O. Møller & Margrethe Simesen: *Acta medica Scandinav.* CXII, fasc. V, 1942. — Kirkegaard, Aage: *Ugesk. f. læger* 108: 423, 1946. — Kirkegaard, Aage: *Den svære akute barbituratsforgiftning* (Diss.) Copenhagen 1951. — Lous, P., Hertel Wulff, E. Trier Mørch & J. M. Sonne: *Ugesk. f. læger* 111: 349, 1949. — Nilsson, Eric: *Acta medica Scandinav. Suppl.* 253, 1951.

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The Anurias Following Kidney Transplantation.

By

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(Submitted for publication August 4, 1953.)

Clinical interest in the possibility of permanent survival of homotransplanted kidneys is real and, of necessity, exacting in its demands. Nothing short of a well-functioning kidney can be of any value to the clinician. In the past, attention has been focussed almost entirely on the obscure immunological problems involved in the homotransplantation of tissues. Transplantation of whole organs presents one with technical problems whose very existence could never be suspected from the rather unreal techniques of implanting small slices of organs in the subcutaneous tissues of rodents. The kidney is a complex organ and it is not surprising that some technical problems have arisen in the course of transplanting a considerable number in this laboratory. Perhaps the most important of these, from a clinical point of view, is the failure of a kidney to secrete after transplantation.

It is of some importance to recognise at least four types of anuria following auto- and homo-transplantation of kidneys in dogs:

Type 1. Failure to secrete after the establishment of the new circulation; this occurs in both auto- and homo-transplanted kidneys and has been previously referred to as the «anuric kidney» (Dempster, 1953 a).

Type 2. An anuria following a period of poor secretion and associated with the toxic syndrome (Dempster 1953 b). This may manifest itself at any time between 24 and 48 hours after transplantation. Immunological factors would not appear to play any part in this anuria as it was found in autotransplanted kidneys.

Type 3. An anuria which occurs in homotransplanted kidneys («first» kidneys — Dempster 1953 a) at a varying interval after transplantation and following a period of good secretion. It is of abrupt onset in that the anuria is established over a period not exceeding 12 hours and often under 6 hours. This anuria is assumed to be the result of an antigen-antibody reaction but the sites of union of the antigen and the antibody have not yet been demonstrated. The exact cause of this anuria has not been established but it is closely related to an irreversible spasm of the intrarenal components of the renal artery (Dempster, 1953 d). While

the generalised arterial spasm can be easily demonstrated in the homotransplanted kidney by arteriograms, other factors would appear to be at work (as a consequence of histamine liberation, for example), which lead to a progressive, rapid lysis of the renal parenchyma. This anuria is also associated with a toxic syndrome in a large percentage of cases; the two factors of anuria and toxic syndrome have been taken as indicators of imminent disintegration of kidney homotransplants (Dempster 1953 a). Some aspects of the factors relating to anuria Type 2 and anuria Type 3 and their association with a toxic syndrome have been discussed elsewhere (Dempster 1953 b).

Type 4. An anuria which occurs within a few hours of homotransplanting the «second» kidney from the same donor to the same recipient as received the «first» kidney. The anuria follows a few hours of secretion and is associated with severe and widespread disintegration of the renal parenchyma (Dempster, 1953 d, Figs. 10 and 11). Again, this reaction is assumed to be due to a severe antigen-antibody reaction and is closely related to intense, generalised intrarenal arterial spasm. A similar reaction has been demonstrated in «first» kidneys which have followed primary sensitisation with skin homografts (Dempster 1953 c). This type of anuria is of experimental interest only.

The anuria with which the present paper is mainly concerned is the first of the four — Type 1 or the «anuric kidney». As this type of anuria occurs in both auto- and homo-transplanted kidneys, it would not appear to involve an immunological phenomenon although this latter factor cannot be entirely ruled out. As this type of anuria has so far proved to be quite unpredictable in its occurrence, it is of some clinical importance to those who wish to continue transplanting kidneys in humans.

In the ordinary course, a transplanted kidney starts secreting clear, dilute and copious urine within ten minutes of establishing a new circulation. Occasionally, in spite of what would appear to be an adequate circulation (Fig. 1 A), a transplanted kidney fails to secrete, or in some cases secretes less than 50 ml in the first twenty-four hours. In a series of auto-transplanted kidneys, the author recorded a 5 % incidence (Dempster 1950); in a series of homotransplanted kidneys a 16 % incidence of anuria was recorded (Dempster 1953 a). Recent experiments show a slight decrease in the incidence of Type 1 anuria and this may be related to increased speed in removing kidneys. Type 1 anurias were not investigated or fully documented until several had been experienced and after it was realised that mere improvement in operative technique would not entirely remove this complication.

In a recent case of Type 1 anuria, an arteriogram on the third day (Fig. 2) showed cortical ischaemia. It was thought that Priscol might have some effect in relieving this cortical ischaemia and accordingly an injection of Priscol was given. It was surprising to find that Priscol produced further spasm of the renal arteries (Fig. 3), without, however, completely closing down any vessel. A brief reference to the effect of Priscol on the renal circulation of the dog will be included in this paper along with some observations on the renal circulation of the dog under certain abnormal conditions.

It should be appreciated that Type 1 anuric kidneys were accidental findings in experiments designed for the purpose of studying the behaviour of the transplanted kidney. Accordingly, there was no formal investigation of Type 1 anuria as such.

Arteriograms were made on seven Type 1 anuric kidneys by injecting Thorotrast into the carotid artery which was anastomosed to the renal artery. Priscol (Ciba Products Ltd. — 1 ml = 25 mg) in varying doses (0.3, 0.5, 1 ml) was injected either intravenously or intra-arterially. Arteriograms were made at 3, 5, 10 and 15 minutes after the injection. In some cases arteriograms were taken some hours after the injection of Priscol. The effect of Priscol at each dose level was repeated at least twice in different kidneys. Normal, autotransplanted and homotransplanted kidneys were used. The technique of making arteriograms of normal kidneys was as follows: a catheter was passed via the right carotid artery to the origin of the renal arteries, and arteriograms taken with the kidneys in situ (Figs. 5 and 6). Blood pressure recordings were taken during all Priscol experiments.

Results.

Total number of kidneys: autotransplants: 18
homotransplants: 12

In both auto- and homotransplanted kidneys three histological groups could be defined:

1. Those kidneys showing little change beyond generalised cloudy swelling of the tubule cells and a few casts in the distal tubules and collecting tubules:

auto: 8

homo: 2

2. Those kidneys showing universal or focal necrosis which was sometimes associated with interstitial oedema and/or casts in the distal tubules;

auto: 4

homo: 6

3. Those kidneys showing widespread casts in both proximal and distal tubules and associated with some empty, dilated distal tubules:

auto: 6

homo: 4

In Group 2, the cortex was always the most severely damaged area (Fig. 7). In most cases, the medulla was fairly healthy although scattered areas showed tubular desquamation. In Groups 2 and 3 there was often an associated congestion and interstitial oedema and free haemorrhage. In Group 2 the tuft capillaries were sometimes dilated and in others spastic. Usually dehaemoglobinised red cells could be seen in the tuft capillaries. Occasionally, in homotransplants, focal necrosis could be seen in the tufts. Thrombosis of the renal vessels was not seen. There was usually a precipitate in the subcapsular space of the glomerulus. Sloughing of the tubular epithelium was evident in some cases. No polymorph zone, no pigmented casts and no basophil interstitialitis were observed. The proximal tubule damage was usually more severe and more extensive than distal tubule damage. Syncytial formation was obvious in some cases (Fig. 12, Dempster 1953 a). In Group 3 the most striking feature was widespread cast formation mainly in the distal tubules (Fig. 8). Associated features were interstitial oedema and/or small foci of tubular necrosis.

(2) 60—72 hours after transplantation.

There were two homotransplanted kidneys in this category. Both showed dilated tubules, some casts in the cortico-medullary zone and in the medulla. There was some cloudy swelling of the tubule cells. The glomeruli were enlarged. The usual immature plasma cell reaction was present.

(3) About 96 hours after transplantation.

There were two homotransplanted kidneys in this category. One showed areas of focal necrosis with a violent polymorph infiltration. The other showed widespread cast formation, small foci of necrosis and a well-established immature plasma cell infiltration.

Arteriograms.

If kidneys are secreting, arteriograms taken within an hour of transplantation show normal cortical filling. Arteriograms of Type 1 anuric kidneys vary soon after transplantation. In seven cases of Type 1 anuria three showed fairly good cortical filling, one showed a curious blurring of the renal vessel outline (Fig. 1 b) which was not visible in arteriograms taken some days later, one showed complete cortical ischaemia, and two showed poor cortical filling. Arteriograms

of Type 1 anuric kidneys at 48, 60 and 90 hours always showed severe arterial spasm with a virtual cortical ischaemia.

The vasoconstrictive effect of Priscol was established in three minutes after its injection intravenously but was maximum at about ten minutes.

Discussion.

Experience in transplanting kidneys will convince one of the reality of Type 1 anuria. Even after considerable experience, I am unable to guarantee that any given kidney will secrete after being transplanted. It would follow that one should take the possibility of the occurrence of Type 1 anuria into consideration before recommending kidney homotransplantation in the human. In fact, our knowledge of the behaviour of the transplanted kidney is so fragmentary at the moment, it would not seem to be profitable to transplant kidneys in humans.

There are certain rather ill-defined signs which can be seen immediately after releasing the new circulation, which give one the impression that any given transplanted kidney will not secrete. These signs are:

1. The ureter does not perform active vermiform movements. One feels confident of success if, within ten minutes of opening the new circulation, the ureter undergoes active peristalsis.

2. The ureter does not swell up or bleed profusely from its cut end. The swelling of the ureter of the transplanted kidney has been described elsewhere (Dempster 1950).

3. The normal tension in the kidney is not attained. The kidney remains rather soft and one can observe that the pulsations of the renal artery are not as robust as usual. The kidney retains its red colour, however, as the capsular artery comes off the main renal artery before entering the kidney. The external colour of such kidneys gives one no clue as to the degree of the intra-renal ischaemia.

Arteriograms were made of only seven Type 1 anuric kidneys and so one is not able to generalise on the nature of the renal circulation soon after transplantation. Three anuric kidneys revealed fairly normal arteriograms soon after transplantation but later on (3rd and 4th days) cortical ischaemia was evident (Figs. 1 A—4). In one instance there was complete cortical ischaemia soon after transplantation. Others were intermediate between these two extremes. It would appear, therefore, that the state of the renal circulation in Type 1 anuric kidneys varies from case to case and this provides some explanation of the histological variation. The blurring of the renal vessels in some anuric kidneys requires further investigation (Fig. 1 B); it may be an artefact due to kidney movement during the exposure.

There is no factual data to support the assumption that some degree of cortical ischaemia was present in all kidneys at some period immediately following release of the new circulation. There is, however, definite evidence that, just prior to the removal (some days later) of Type 1 anuric kidneys, a cortical ischaemia was present; but this is evidence only at one point in time. There is evidence

in one case that on the 3rd and 4th days of anuria the same degree of cortical ischaemia was found in arteriograms taken on successive days (Figs. 2 and 4). The available evidence suggests, therefore, that some factor causes arteriolar spasm of varying degree soon after releasing the new circulation and this is the cause of some cases of Type 1 anuria.

It was due to the fact that cortical ischaemia was recognised in Type 1 anuric kidneys that Priscol came to be used in these experiments. There was no indication in the literature that Priscol was vasodilator to the renal vessels, but a priori it was assumed to be. The first injection was made into the carotid artery anastomosed to the renal artery of the transplanted kidney. It was an unexpected result to find that Priscol increased the renal arterial spasm already present. In other experiments Priscol was given in smaller doses and intravenously; doses of 0.3 ml also produced renal arterial spasm (Figs. 9 and 10). It is to be noted that even with severe spasm following Priscol a cortical flow can occur and urine production continues; there is no evidence that Priscol completely shuts down the afferent arterioles. The duration of the Priscol effect has not been precisely determined. Evidence from two secreting kidneys is the following: the intense constriction is still present 60 minutes after the injection, at 90 minutes it is less intense and at 150 minutes there is only slight recovery. It is known that 24 hours after the injection of Priscol the renal circulation has resumed its previous appearance (Figs. 2 and 4). There was no evidence that small intravenous doses of Priscol dilated the renal vessels. Normal kidneys responded in a manner similar to transplanted kidneys after injections of Priscol (Figs. 5 and 6).

Neither auto- nor homo-transplanted kidneys, in which Type 1 anuria occurred, showed any significant relation to the histological features of human cortical necrosis (Fig. 11); this is perhaps due to the fact that no re-establishment of an outer cortical circulation occurred. Neither did the histology of Type 1 anuria resemble that of Type 3 anuria (Fig. 12). If a homotransplanted kidney is left in the host for 24—48 hours after Type 3 anuria sets in, the renal parenchyma disintegrates rapidly and at a pace far greater than can be attributed to ischaemia alone (Fig. 12) — if one can assume that cortical necrosis is due mainly to vascular spasm. This was not the case with Type 1 anuric kidneys in which even after four days of anuria the renal parenchyma was in a fair condition. It would appear, therefore, that associated with the generalised vascular spasm in Type 3 anuria, there are lytic processes going on which rapidly destroy the renal parenchyma. The lytic factors may be due to histamine release as a consequence of the union of antigen and antibody in the kidney. It is important, therefore, to remove homotransplanted kidneys as soon as possible after the onset of Type 3 anuria otherwise their histology becomes hopelessly obscured. Type 3 anuria is the natural termination of the life of a homotransplanted kidney and it should be realised that by the time this anuria occurs irreversible parenchymal damage usually has already occurred. There is no possibility of such a kidney secreting again.

Homotransplanted kidneys usually show signs of immature plasma cell im-

filtration from the third day after transplantation (Dempster, 1953 a). Of the four homotransplanted kidneys which were anuric for 3—5 days, three showed signs of immature plasma cells. The fourth kidney was diffusely necrosed, and the plasma cell reaction was absent. It would appear, therefore, that even if the homotransplanted kidney is not functioning as a physiological unit its reticulo-endothelial system is still able to react against the host serum — provided such serum is actually coursing through the kidney interstitium. It has already been indicated (Dempster, 1953 a) that the plasma cell reaction is confined to the cortex of the homotransplanted kidney. In the presence of severe cortical ischaemia a generalised plasma cell reaction could hardly be expected to occur. The fact that a medullary circulation may be maintained is of no consequence so far as the plasma cell reaction is concerned. It would appear, therefore, that unless a transplanted organ or tissue is receiving an adequate blood supply and is metabolising normally, it will not reveal the mechanism of its normal response to a new environment nor will it react against the serum of its host. This perhaps explains why after many years of careful research into the effects of implanting small pieces of organs in rodents, no one has observed that a homografted organ reacts as vigorously against the host serum as the host's reticulo-endothelial system reacts against the organ.

The anuria (Type 2) associated with a toxic syndrome is not always easily explained. It has been shown elsewhere (Dempster 1953 b) that autotransplanted kidneys may fail on account of vascular accidents and may show three types of necrosis — general, polar and focal. It is obvious that anuria would result from the general type of necrosis. It is not easy to understand why anuria should also occur in the polar and focal types of necrosis in which larger areas of the kidney remain healthy.

Type 4 anuria is associated with severe glomerular damage and generalised arterial spasm of varying degree (Dempster 1953 a, Figs. 516—519; Dempster, 1953 d, Figs. 10 b and 11). »Second» kidneys always secrete normally after establishing the new circulation but some hours later sudden anuria occurs. If arteriograms are taken an hour after transplantation at a time when the kidney is secreting they appear normal; if arteriograms are taken soon after the onset of anuria cortical ischaemia or generalised vascular spasm is found (Dempster 1953 d, Figs. 10 a and b, and 11).

The Cause of Type 1 Anuria.

Among many possible causes, two may be selected for special attention:

1. Arteriolar spasm.
2. Damage to the filtering mechanism.

1. *Arteriolar spasm.*

Arteriolar spasm may be initiated by direct nervous irritation during removal of a kidney. There is some evidence for the factor of nervous irritation: Houck (1951) stimulated the nerves on the renal artery and produced afferent arteriolar

constriction severe enough to be visible as infarets. If one assumes that afferent arteriolar spasm was incurred during the removal of the kidney, one must also assume that the act of denervation (*i. e.*, in removing the kidney) and the twenty minutes complete ischaemia in no way reversed the spasm. There is no factual evidence in the present material which strongly confirms such an assumption. On the assumption that nervous stimulation initiated arteriolar spasm, a policy of quick removal of kidneys was instituted in this laboratory. This policy reduced but has not eradicated Type 1 anuria. The fickleness of the renal circulation leaves one in a cloud of ignorance. However, certain facts have arisen from the material so far collected:

1. The blood flow through anuric kidneys is usually markedly reduced.
2. Where cortical ischaemia exists, there may be a juxtamedullary cortical circulation. This latter pathway does not necessarily represent an alternative pathway for the previous *normal* renal blood flow. When cortical ischaemia exists, there is an increased renal peripheral resistance which usually affects the whole of the renal vasculature. The previous total blood flow is then reduced and what flow there is takes the only path open to it, which happens, in most cases, to be the juxtamedullary vessels; in very severe conditions of intra-renal spasm even this pathway is closed and blood enters the main branches of the renal artery and, from there in some way presumably gets into the venous side (See Fig. 2, Dempster, 1953 d). This latter statement is an assumption. Venous filling has not been demonstrated in cases of severe spasm as indicated in Fig. 2 (Dempster 1953 d). However, on cutting the renal vein a small trickle of blood does emerge (10 ml/minute being the lowest recording).

The »Oxford shunt« is perhaps too mechanical a concept to fit the infinite number of variations to which the renal circulation may be subjected. From the small selection of arteriograms presented in this paper, one can draw certain conclusions about the renal circulation in transplanted kidneys which may have a bearing on the possible circulatory variations in the normal kidney:

1. There may be a normal renal blood flow in which case there is normal cortical filling.
2. There may be a reduced renal blood flow with fairly good cortical filling and known to be associated with Type 1 anuria but usually with secretion (Fig. 1 A).
3. There may be a severely reduced renal blood flow with surprisingly good cortical filling and known to be associated with urine formation (Figs. 6 and 10). Renal vascular spasm does not necessarily imply only afferent and/or efferent arteriolar spasm.
4. Where there is cortical ischaemia there is usually a reduced renal blood flow (Figs. 2 and 4) even if generalised vascular spasm is not present; the reverse is not necessarily true.
5. Afferent arteriolar spasm is not necessarily related to nervous stimulation. Some anuric kidneys have shown a fairly normal arteriogram within an hour after transplantation (Fig. 1) and at a later date afferent arteriolar spasm has set in (Figs. 2 and 4). Type 3 anuria is always associated with a generalised vascular spasm (Fig. 13) which may manifest itself at any time up to 18 days after

transplantation — and hence, 18 days after denervation. Sympathetic block and spinal anaesthesia, therefore, would seem to be ineffective measures to be employed in human acute anurias. Afferent arteriolar spasm, then, may be due to many causes — one of which may be nervous stimulation. The »Oxford shunt» supporters have perhaps exaggerated the rôle of nerve stimulation in producing renal vascular spasm and cortical ischaemia; furthermore, one is left in ignorance of the duration of the effects of such nerve stimulation, the nature of the renal damage if any which ensues, and the renal blood flow before and after such stimulation. Block et al. (1952) failed to produce anuria or oliguria for longer than 70 minutes following electric stimulation of the renal nerves.

Selkurt (1945) has shown that following an interval of complete renal ischaemia, a period of increased renal vascular resistance ensues. As evidence of this there was found to be a reduction of the actual blood flow which persisted for some considerable time. Selkurt (1945) was of the opinion that following periods of ischaemia renal vascular resistance was mainly due to arteriolar resistance. So far as transplanted kidneys are concerned, there is always a reduced blood flow for some hours after releasing the new circulation but even renal blood flows of 1.5 ml/min./gram of fresh kidney (normal: 3—4 ml/min./gram fresh kidney) are compatible with urine production and fairly good cortical filling. On the other hand, there may be an individual variation in which arteriolar spasm is more violent and persists for sufficiently long as to become irreversible and that this is the cause of Type 1 anuria in certain cases. The histological evidence is in accord with some aspects of the description given of acute cortical necrosis (Sheehan and Moore, 1952).

2. *Damage to the filtering mechanism.*

Sheehan and Moore (1952) have placed the filtering mechanism high on their list of the gradient of sensitivity of renal tissues to ischaemia. Without producing much in the way of experimental evidence to support their claim, they argue that half an hour of ischaemia is sufficient to damage the integrity of the filtering mechanism. One can spend half an hour transplanting a kidney and within ten minutes of releasing the new circulation the kidney secretes copious urine with a high protein content. This increased proteinuria is transient and within two hours has disappeared (these experiments will be presented elsewhere). It may quite well be that individual variation produces more than average damage to the filtering mechanism and widespread cast formation results. The casts later block the tubules and, using a concept of Woods (1946), the sudden alteration of relative pressures in the inter-tubular capillaries and the cast-laden tubules leads to rupture or congestion of the former and interference with the renal circulation naturally follows. This sequence of events could explain some cases of Type 1 anuria in transplanted kidneys.

The Relationship of Type 1 Anuria to Immunological Factors.

There is no evidence that any immunological factor is involved. There is some evidence which points rather to technical and against immunological factors. It

is indicated elsewhere (Dempster, 1953 a, Table 5) that «first» kidneys removed after 24 hours did not appear to immunise the hosts against «second» kidneys from the same donors transplanted some days later. If the «first» kidneys had immunised the hosts, it is most unlikely that the «second» kidneys would have escaped an immediate immunity reaction. It will be shown, however, in a subsequent paper that 24 hours is sufficient time to initiate some change in the host.

The sole criterion of success of a transplanted organ, from a clinical point of view, is functional efficiency. Biologists, in the past, however, have often been quite satisfied with some vague sort of histological survival of pieces of organs implanted in the subcutaneous tissues. Type 1 anuria, especially Group I, shows that what appears to be histological survival is not significant in itself. Furthermore, the kidney autotransplanted to the neck of dogs is unable to concentrate the urine it excretes although histologically the kidney appears normal. The present account of anuria serves to emphasise the need for further animal experiments before human experiments can be carried out with any degree of confidence.

Summary.

Four types of anuria following kidney transplantation have been described. Type 1 anuria occurs in auto- and homotransplanted kidneys and constitutes a serious technical problem. No immunological factor would appear to be involved.

The histological features of kidneys which have been removed on account of Type 1 anuria have been described. Three groups have been defined:

1. Cloudy swelling of tubule cells.
2. Generalised or focal tubule necrosis.
3. Widespread cast formation.

Some possible causes of Type 1 anuria have been discussed. Reference has been made to the renal vasoconstrictive effects of Priscoll.

Acknowledgements.

I am grateful to Dr. B. Lennox for his opinion on the histological findings. The photomicrographs are by Mr. E. V. Willmott. I am indebted to Dr. I. Doniach for Figure II. The expenses involved in transplanting kidneys were defrayed by a grant from the Medical Research Council.

References.

1. Block, M. A., Wakim, K. G. and Mann, F. C. 1952 *Amer. J. Physiol.* 169, 679. — 2. Dempster, W. J., 1950: *Ann. Roy. Coll. Surg. Eng.*, 7, 275. — 3. Dempster, W. J., 1953 (a): *Brit. J. Surg.*, 40, 447. — 4. Dempster, W. J., 1953 (b): *Acta med. Scand.*, 144, 360. — 5. Dempster, W. J., 1953 (c): *Brit. J. Plast. Surg.*, 6, 228. — 6. Dempster, W. J., 1953 (d): *Arch. Inter. Pharmacodyn. Thérap.* In press. — 7. Houck, C. R., 1951: *Amer. J. Physiol.*, 167, 523. — 8. Selkurt, E. E., 1945: *Amer. J. Physiol.*, 145, 376. — 9. Sheehan, H. L. and Moore, H. C., 1952: *Renal Cortical Necrosis of the Kidney and Concealed Accidental Haemorrhage*. Blackwell Scientific Publication, Oxford. — 10. Woods, W. W., 1916: *J. Path. Bact.*, 58, 767.



Fig. 1 A. Renal arteriogram taken 30 minutes after homotransplantation. The renal tree and the cortical filling appear to be normal. This kidney was anuric. Systolic blood-pressure 120 mm Hg.



Fig. 1 B. Renal arteriogram taken 60 minutes after homotransplantation. The renal vessels are blurred but cortical filling appears normal; this would appear to be an artefact. This kidney was anuric. Systolic bloodpressure 125 mm Hg.



Fig. 2. Arteriogram of the kidney presented in Fig. 1 A taken on the third day after homotransplantation. The kidney is much enlarged, as is usual after transplantation. There is cortical ischaemia and some general arterial spasm. This kidney was still anuric. Systolic bloodpressure 110 mm Hg.



Fig. 3. Arteriogram of the kidney presented in Figs. 1 and 2, 10 minutes after an intra-arterial injection of Priscol. There is considerable spasm of the whole renal arterial tree, but no evidence of complete shut down of any vessel. Systolic bloodpressure 110 mm Hg.



Fig. 4. Arteriogram of the kidney presented in Figs. 1 A, 2 and 3, on the fourth day of anuria. The spasm induced by Priscol has disappeared and the renal arteriogram now resembles that of Fig. 2. Systolic bloodpressure 110 mm Hg.



Fig. 5. Arteriogram of a normal left kidney in situ. Systolic bloodpressure 80 mm Hg.



Fig. 6. An arteriogram of the kidney presented in Fig. 5, ten minutes after an intra-aortic injection of Priscol. There is considerable arterial spasm involving the whole of the renal arterial tree. Systolic bloodpressure 100 mm Hg: the pressure rose after the Priscol injection.

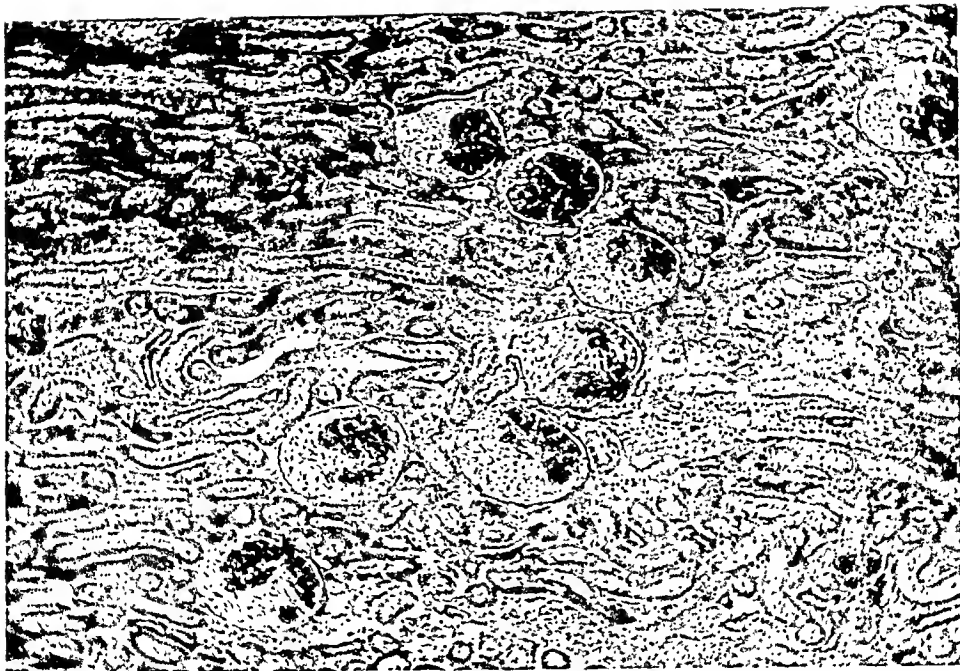


Fig. 7. A photomicrograph of a section from an autotransplanted kidney which was anuric for 36 hours (Type 1 anuria). Widespread tubular necrosis and oedema are obvious. H. and E. $\times 95$.

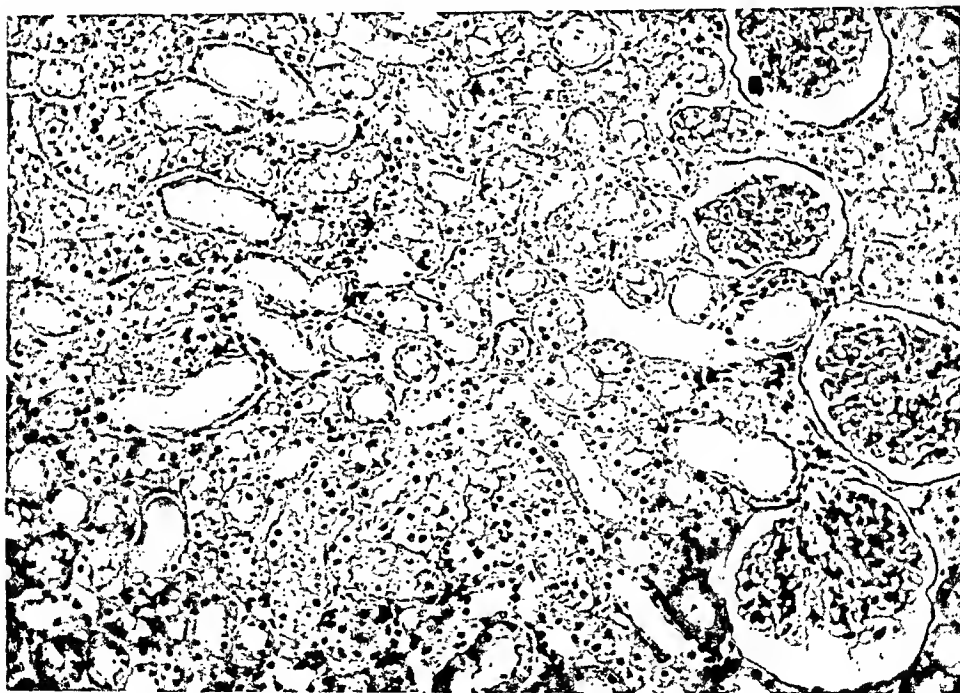


Fig. 8. A photomicrograph of a section from an autotransplanted kidney which was anuric for 48 hours (Type 1 anuria). Widespread tubular cast formation is a striking feature. H. and E. $\times 190$.

DEMPSTER: The Anurias Following Kidney Transplantation.



Fig. 9. An arteriogram of a kidney 30 minutes after homotransplantation. The adrenal gland was transplanted with the kidney and a small renal twig can be seen supplying a segment of the adrenal. Systolic blood pressure 100 mm Hg.



Fig. 10. An arteriogram of the kidney presented in Fig. 9, 10 minutes after an intravenous injection of 0.3 ml Priscol. There is considerable arterial spasm affecting the whole of the renal arterial tree. Systolic blood pressure 100 mm Hg. Urine production continued as cortical filling did not appear to be markedly impaired. Thus, Priscol would not appear to be acting severely on the afferent arterioles.

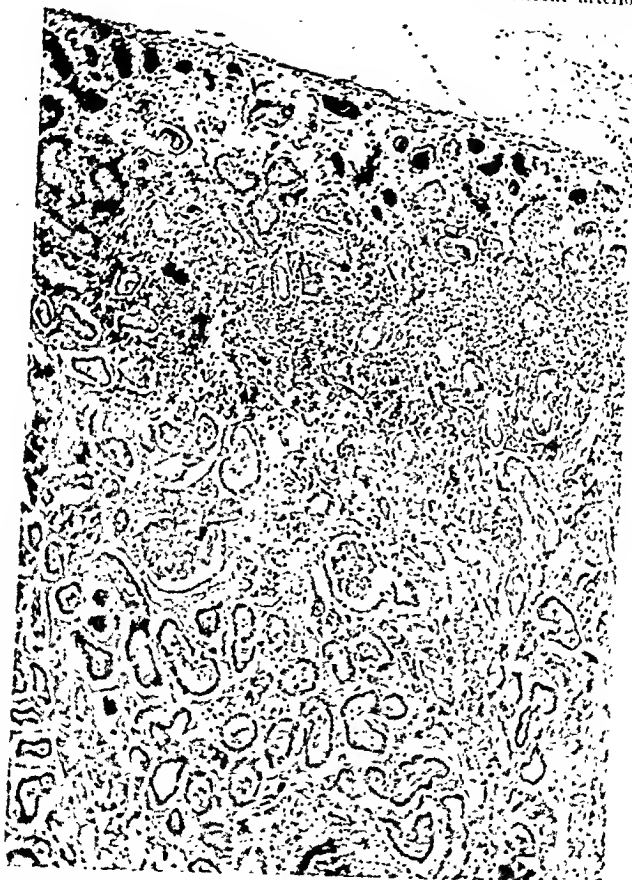


Fig. 11. A photomicrograph of a section of a human kidney showing cortical necrosis. The patient was anuric for 6 days before death ensued. H. and E. $\times 95$.

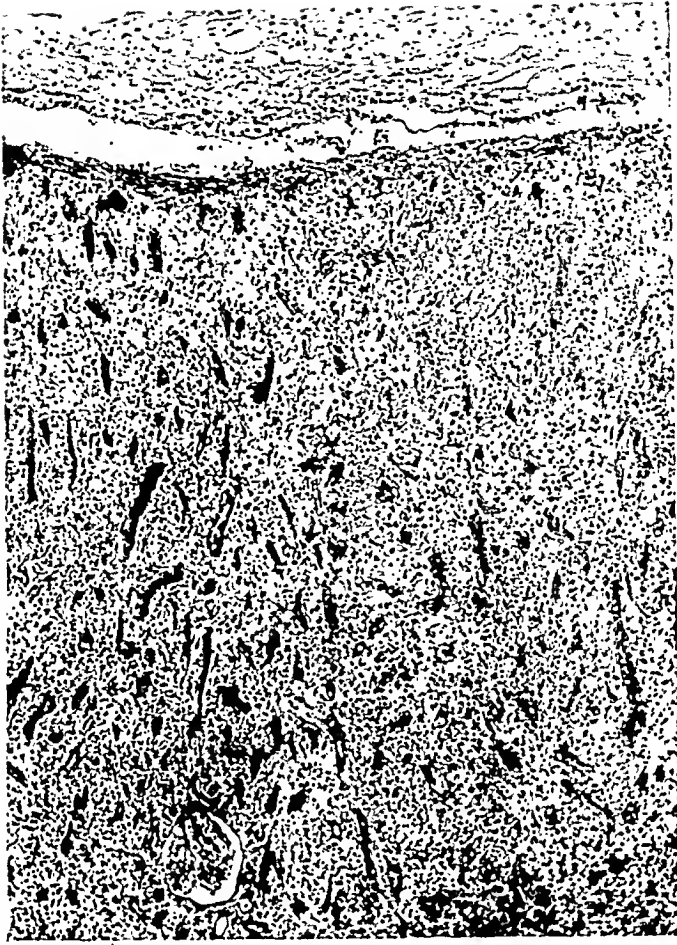


Fig. 12. A photomicrograph of a section taken from a homotransplanted kidney. The kidney was removed 36 hours after Type 3 anuria occurred. There is widespread parenchymal lysis. H. and E. $\times 105$.



Fig. 13. An arteriogram of a homotransplanted kidney which, after secreting well for several days, suddenly became anuric (Type 3). The general arterial spasm is typical of the terminal phase of first homotransplanted kidneys. Once this type of arterial spasm is established, it is irreversible.



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The Electrocardiogram in Tobacco Smoking during Hypoxia.

A Preliminary Account.

By

BERTIL von AHN.

(Submitted for publication August 10, 1953.)

On tobacco smoking under ordinary circumstances, a slight flattening of the T-waves of 1—2 mm or less develops and, simultaneously, an increase in the heart rate of 10—20 beats per minute (1, 2, 3, 4, 5, 6, 7, 8, 9). This holds true both for smokers and non-smokers and for individuals both with healthy and diseased hearts. Similar ECG changes have been observed following injection of nicotine (10). In young individuals (2) and individuals with neurocirculatory asthenia tobacco may produce a more pronounced tachycardia with resultant greater decrease in the height of the T-waves. It should be pointed out, that this reduction in amplitude nearly always occurs in connection with an increase in the heart rate. ECG changes on smoking are of the same type as is seen in increased sympathetic tone. Previously, they were, probably erroneously, regarded as the result of impaired coronary circulation or a toxic effect upon the myocardium. It is very improbable that tobacco smoking, at least in individuals with healthy hearts, should be able to disturb the normal balance between the work of the heart and the coronary circulation. The healthy heart has an impressive coronary reserve, which even with greatly increased work of the heart compensates the increased oxygen requirement of the myocardium. Similarly, the coronary reserve may be reduced considerably before the function of the heart substantially deteriorates and pathological ECG changes develop. Wegria et al. (11) in experiments on dogs showed that reduction of the coronary circulation of 10—35 %, as a rule, did not produce any ECG changes. At a reduction

of 35—70 %, as a rule, «slight» ECG changes developed. At a reduction of 70—100 % the changes were always pronounced.

Previously, it has been maintained by many authors that tobacco smoking may release coronary spasm. To support this, in addition to evidence from animal experiments (Morawitz & Zahn (12)), the fact has been stated that tobacco may provoke pain of anginal type («tobacco angina»). This may occur both in individuals with diseased and with healthy hearts. In some few cases it has been demonstrated that the «tobacco angina» is associated with a definite myocardial anoxia (13, 14, 15, 16, 17, 18). In all these cases, patients with coronary disease of the heart and never individuals with healthy hearts have been concerned.

It has not yet been demonstrated that tobacco, as a rule, exerts the same constricting effect upon the coronary vessels as it undoubtedly exerts upon the peripheral vessels.

In order to attempt to obtain some criteria for this hypothetical coronary «nicotine spasm», I have investigated the effect of tobacco smoking on the ECG during hypoxia. May, by smoking during hypoxia, ECG changes be provoked which cannot be produced by smoking under normal circumstances? This problem gains further interest and justification as Bellet et al. (19) showed by experiments on dogs that the effect of tobacco smoking and nicotine was more pronounced on hearts with artificial infarcts than on intact hearts. Dogs with cardiac infarction developed pronounced ECG changes following a dose of nicotine which was only a quarter of that required to produce slight changes in intact animals.

Hypoxia in the myocardium may be thought to develop on account of:

1. organic changes in the coronary arteries.
2. altered haemodynamic conditions.
3. reduced oxygen content in the coronary blood.
4. spasm or reflex constriction of the coronary arteries.

According to Katz (quoted by Jervell (20)), coronary insufficiency is more frequently a sequel of anatomical changes in the vessels and disturbances in the dynamics of the coronary circulation than a sequel of vascular constriction or spasm. The hypothesis of spasm can, however, not be rejected but is, in certain cases, the most probable cause of acute coronary insufficiency (e. g. angina pectoris without simultaneous increase in the heart rate). That coronary spasm actually exists has recently been demonstrated by Spritzler et al. (21) by experiments on dogs.

On inspiration of an oxygen-poor mixture of gases, hypoxia undoubtedly develops in the myocardium and in this way one condition for coronary insufficiency is present. The organism attempts to compensate for the oxygen deficiency by increasing the minute volume among other factors. In hypoxia, the coronary vessels also dilate. Dietrich and Schimert (22) showed, in animal experiments, that induced hypoxia causes increase in the coronary circulation greater than would correspond to the simultaneous increase in the minute volume. If tobacco smoking or nicotine cause any significant constriction of the coronary vessels, this might impede the compensatory dilatation of the coronary vessels.

It is also conceivable that the carbon monoxide contained in the smoke might accentuate the hypoxia in the myocardium.

Material.

The material consists of 46 volunteers, 34 of whom were in the age group 20—26 years (group I), 20 smokers and 14 non-smokers, and 12 in the age group 38—51 years (group II), of whom 2 were non-smokers. All had clinically healthy hearts. In group I, one individual with heart disease is present (case 6). This case was, however, not included in the statistical analysis.

Method.

The smokers abstained from smoking for 3—4 hours prior to each test. Prior to the tests, the volunteers rested for 30—40 minutes on a comfortable couch. Each volunteer underwent at least two hypoxia tests, lasting 19—20 minutes. The first served as a control test. During the second, the volunteers smoked a cigarette or 3—4 cm of a cigar (Flor de Vallez). The first ECG was taken after 6 minutes' hypoxia, when the respiratory rate, the heart rate and the oxygen saturation of the blood had become stabilized at constant levels. During the smoking tests, tobacco smoke was supplied via a special lateral mouthpiece from the 9th to the 17th minutes of the test. Tests were also performed with nicotine (nicotine bitartrate) which was administered slowly intravenously in a dose of 3—5 mg, calculated as pure nicotine. ECGs were taken after 1, 5 and 8 minutes' smoking. In addition to the usual three leads from the extremities, three chest leads were also recorded: CR₂, CR₄ and CR₇. The relative oxygen saturation of the blood was followed continuously by means of an oxymeter, constructed in Sweden (after Millikan). The absolute oxygen saturation of the blood was determined by the Pulfrich Step Photometer, according to Jonxis' method (23). The blood was obtained by puncture of the brachial artery where an artery needle was introduced. Blood samples were taken prior to smoking, between the 7th and 8th minutes of the experiment and immediately after smoking between the 18th and 19th minutes. The error of method in this procedure only attained 0.66 % (percentage of oxygen saturation). Differences in the arterial oxygen saturation of less than 2 % are thus statistically reliable.

The composition of the gas mixture employed was 6.5 % O₂, 4.5 % CO₂ and 89 % N₂ (after Malmström (24)).

Results.

Normally, during the hypoxia test, flattening of the T-waves occurs together with increase in the heart rate, which stabilizes itself at a constant level after about 5 minutes. After the elapse of the same period, the arterial oxygen saturation is stabilized at, on an average, 67 % and thereafter remains constant or

falls further by 2—3 % after 18—19 minutes' hypoxia during the smoking test. With few exceptions, the oxymeter registered the same relative oxygen saturation during both control and smoking tests in the same individual. Thus, tobacco smoking did not tangibly influence the general arterial oxygen saturation.

Group I. Volunteers in the age group 20—26 years.

Cigarette smoking.

In connection with smoking, the heart rate increased by 10—20 beats per minute and the T-waves were further flattened in all leads. In one case only the T-waves became negative (lead II) after smoking. No tangible depression of S—T was observed, nor were any arrhythmiae registered.

Cigar smoking.

As the volunteers absorbed more nicotine and carbon monoxide on cigar smoking than on smoking of cigarettes, more pronounced ECG changes might be anticipated after cigar smoking. During the cigar tests the volunteers smoked, as a rule, 3—4 cm of the cigar (= 2—3 gm tobacco) and thus in the same period they consumed considerably more tobacco than on smoking a cigarette (= 1 gm tobacco).

The ECG changes observed were of the same type as in the cigarette tests, only in some cases more pronounced (see Figures 5 a and 5 b).

Experiments with nicotine.

In the nicotine experiments, the same type of ECG changes were observed as in the smoking experiments. The volunteers did not suffer any inconvenience from the nicotine doses of 3—5 mg which were administered. A slight or moderate, rapidly transient euphoria was common.

Group II. Volunteers in the age group 38—51 years.

Cigar smoking.

In one case only did the heart rate increase tangibly, viz. by 23 beats per minute (case 5, below); in one case the heart rate fell by 13 beats per minute. In the remaining 10 cases, the alteration in the heart remained within the limits —3 to +8 beats per minute.

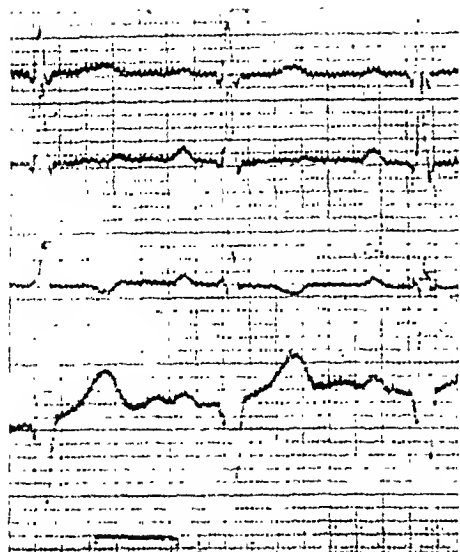
In only one case (case 5) did significant changes occur in the S—T interval and T-waves.

Cigarette smoking.

No changes in the ECG occurred in any of the 7 cases.

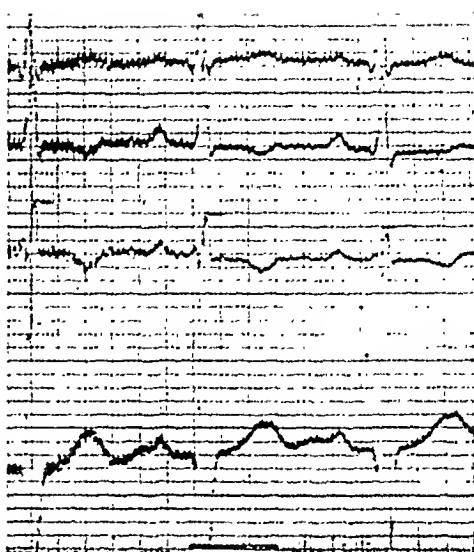
As a rule, the older volunteers reacted much less to tobacco than did the younger volunteers.

Illustrative Cases.



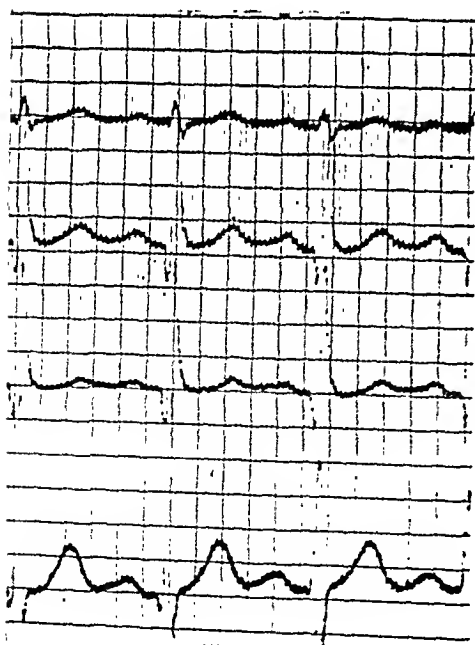
ECG 1 a.

Case 1. Soldier, aged 20 years, healthy heart, non-smoker. ECG 1 a: ECG after 6 minutes' hypoxia and prior to smoking. Heart rate 84 beats per minute. T_2 alternates between diphasic and weakly positive. T_3 negative.



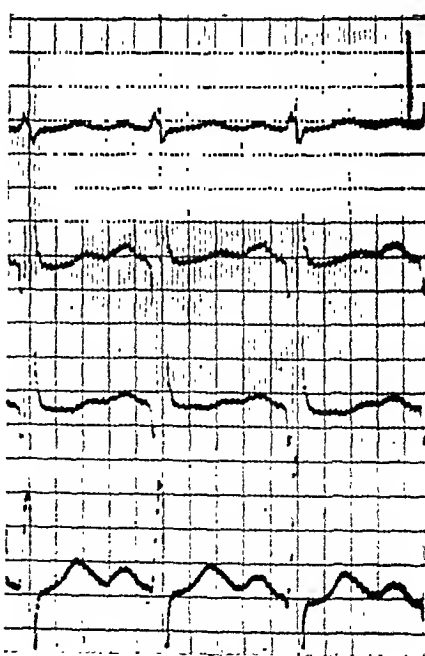
ECG 1 b.

ECG 1 b: ECG after 17 minutes' hypoxia and after smoking a cigarette in 7—8 minutes. Heart rate 92 beats per minute. T_2 alternates between diphasic and negative. T_3 more deeply negative. T in CR₁ flattened.



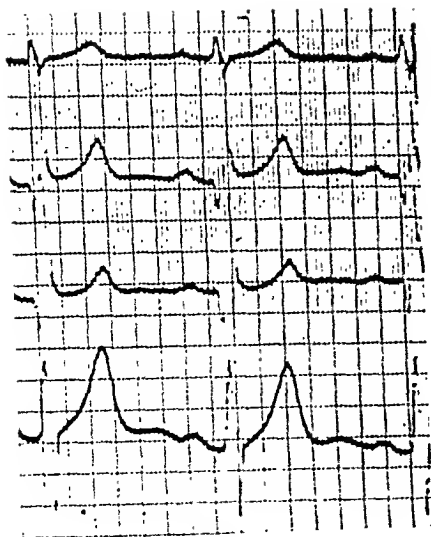
ECG 2 a.

Case 2. Medical student, aged 26 years. Healthy heart. Smoker. ECG 2 a: ECG after 6 minutes' hypoxia prior to smoking. Heart rate 106 beats per minute.

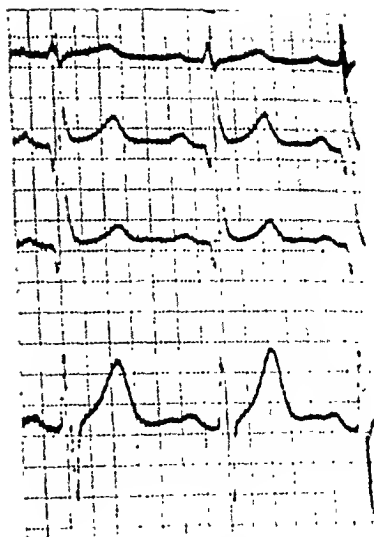


ECG 2 b.

ECG 2 b: ECG after 17 minutes' hypoxia and after 8 minutes' cigar smoking. Heart rate 120 beats per minute. Considerable flattening of T-waves in leads II, III and CR₁.



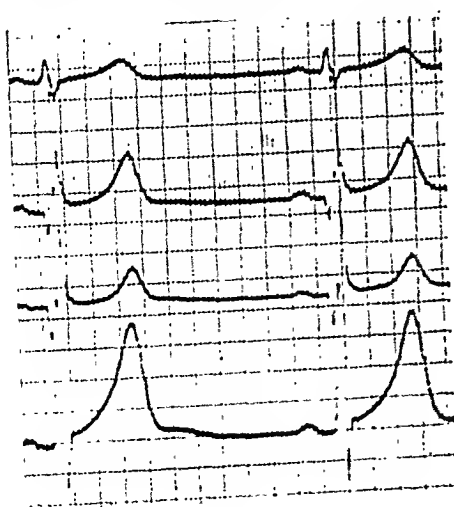
ECG 3 a.



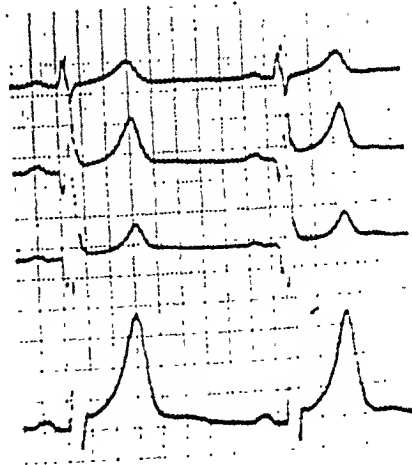
ECG 3 b.

Case 2. ECG 3 a: ECG 12 minutes after intravenous injection of 0.5 mg dihydroergotamine (DHE 45) and after 6 minutes' hypoxia, prior to smoking of cigar. Heart rate 82 beats per minute.

ECG 3 b: ECG after 17 minutes' hypoxia and after smoking cigar. Heart rate 88 beats per minute. Slight flattening of T-waves.



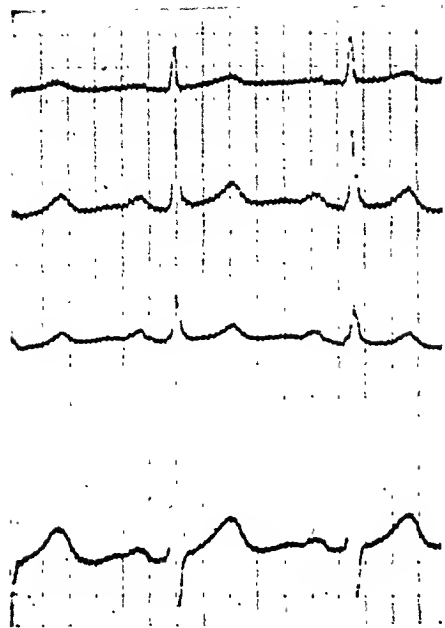
ECG 4 a.



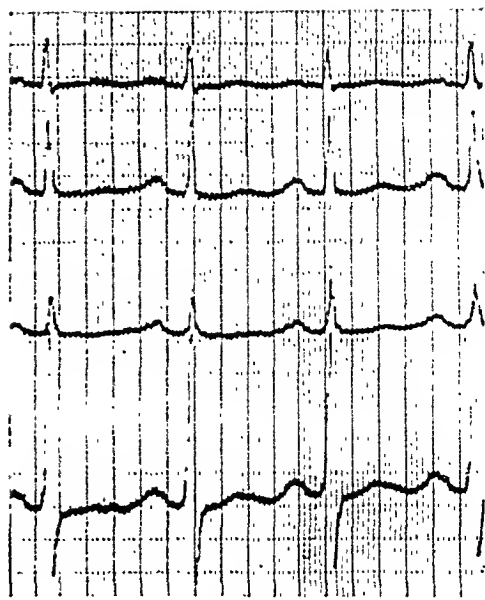
ECG 4 b.

Case 2. ECG 4 a: Resting ECG prior to smoking. Heart rate 52 beats per minute.

ECG 4 b: ECG after 8 minutes' cigar smoking under normal conditions (no hypoxia). Heart rate 65 beats per minute. No substantial changes in the T-waves.



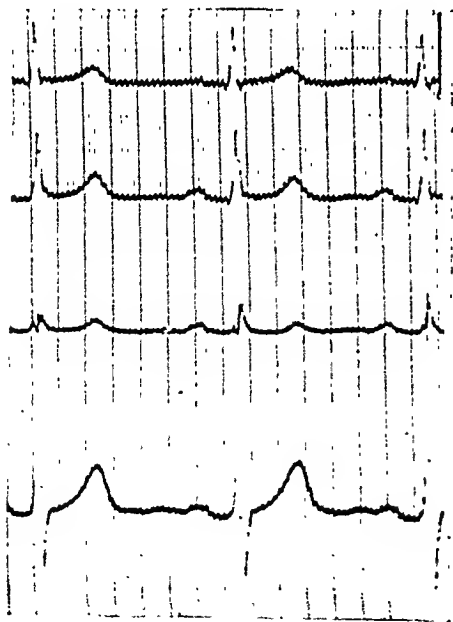
ECG 5 a.



ECG 5 b.

Case 3. Medical student, aged 25 years. Healthy heart. Smoker. ECG 5 a: ECG after 6 minutes' hypoxia. Heart rate 93 beats per minute.

ECG 5 b: ECG after 17 minutes' hypoxia after smoking cigar. Heart rate 115 beats per minute. Marked flattening of all T-waves. S—T depressed in CR₁.



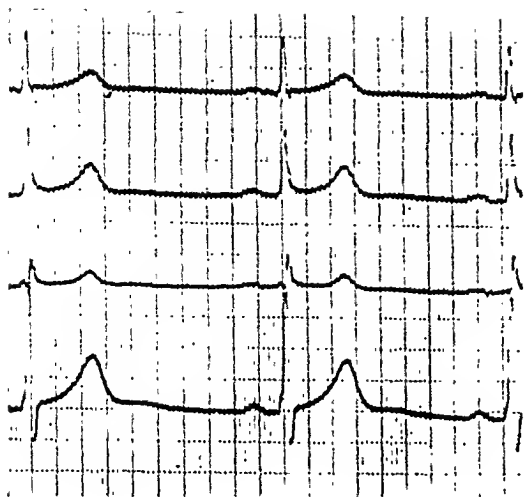
ECG 6 a.



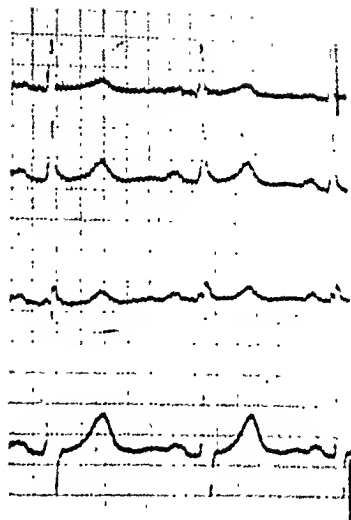
ECG 6 b.

Case 3. ECG 6 a: ECG 12 minutes after 1 mg dihydroergotamine intravenously and after 6 minutes' hypoxia, prior to smoking. Heart rate 85 beats per minute.

ECG 6 b: ECG after 17 minutes' hypoxia and after smoking cigar. Heart rate 93 beats per minute. Slight flattening of T-waves.



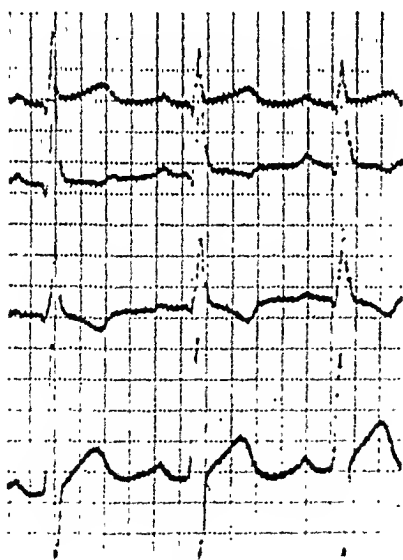
ECG 7 a.



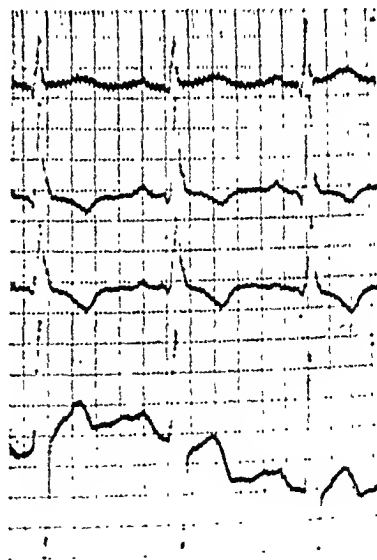
ECG 7 b.

Case 3. ECG 7 a: Resting ECG prior to smoking. Heart rate 61 beats per minute.

ECG 7 b: ECG after 8 minutes' cigar smoking under normal conditions (no hypoxia). Heart rate 89 beats per minute. Slight flattening of the T-waves.



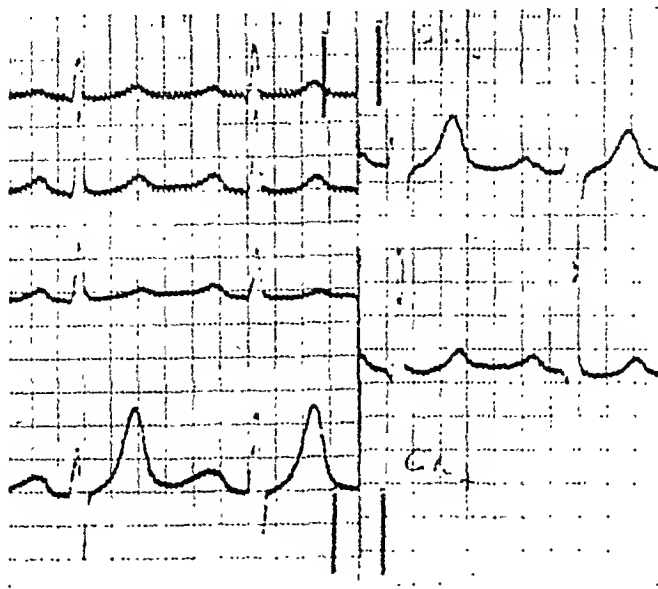
ECG 8 a.



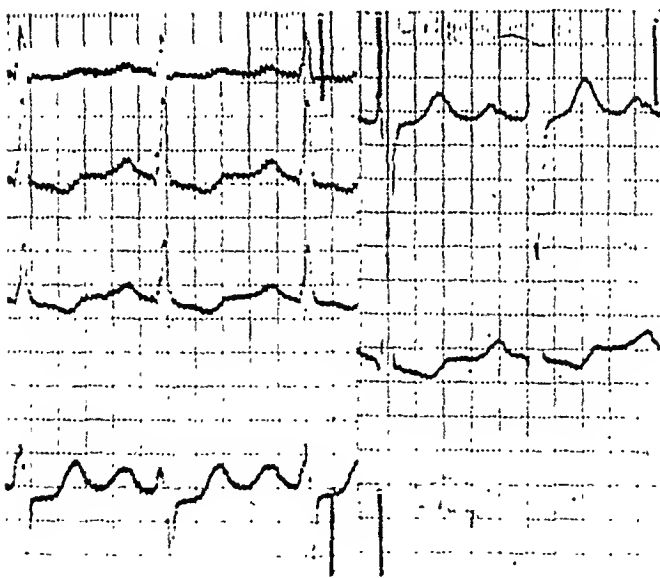
ECG 8 b.

Case 4. Soldier, aged 20 years. Healthy heart. Smoker. ECG 8 a: ECG after 6 minutes' hypoxia. Heart rate 100 beats per minute. T_2 diphasic, T_3 negative.

ECG 8 b: ECG after 17 minutes' hypoxia and after intravenous injection of 3 mg nicotine. Heart rate 101 beats per minute. T_2 negative, T_3 more deeply negative, T_1 flattened.



ECG 9 a.

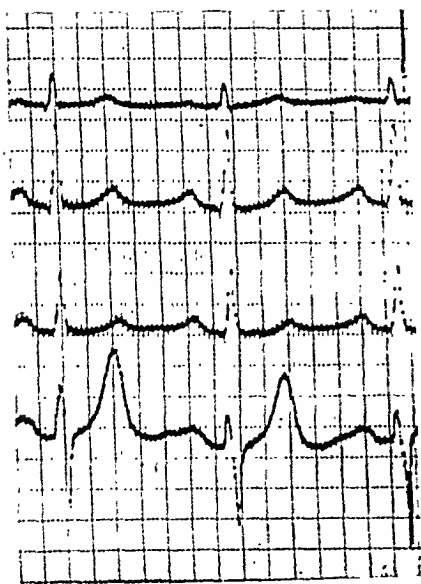


ECG 9 b.

Case 5. Male, aged 38 years. Clinically healthy heart. Non-smoker.

ECG 9 a: ECG after 6 minutes' hypoxia. Heart rate 91 beats per minute. Normal ECG.

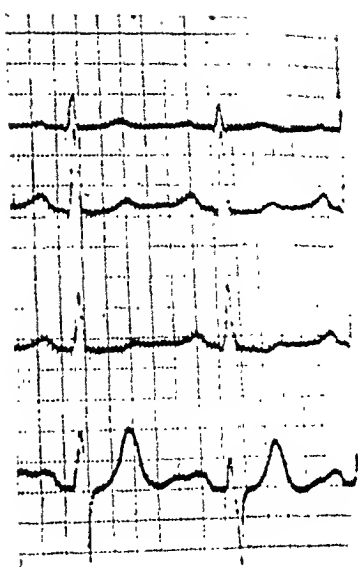
ECG 9 b: ECG after 17 minutes' hypoxia and after cigar smoking. Heart rate 114 beats per minute. T-waves diphasic in leads II and CR, negative in lead III, flattened in lead CR. S-T depressed in all leads.



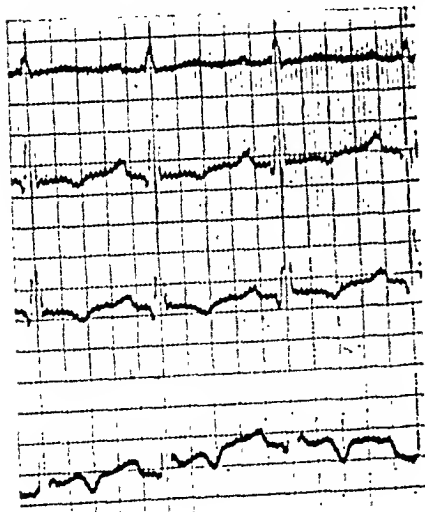
ECG 10 a.

Case 5. ECG 10 a: Hypoxia test without smoking (control test). ECG after 6 minutes' hypoxia. Heart rate 92 beats per minute.

ECG 10 b: ECG after 17 minutes' hypoxia without smoking. Heart rate 90 beats per minute. S—T slightly depressed in leads II, III and CR. Slight flattening of the T-wave.



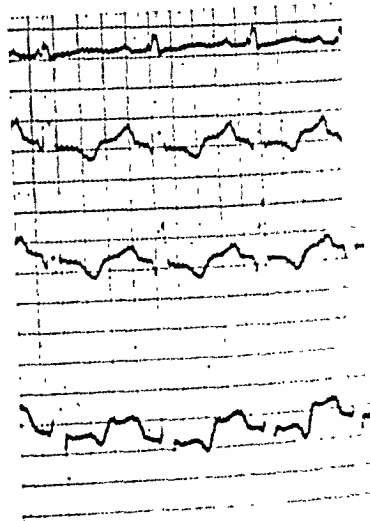
ECG 10 b.



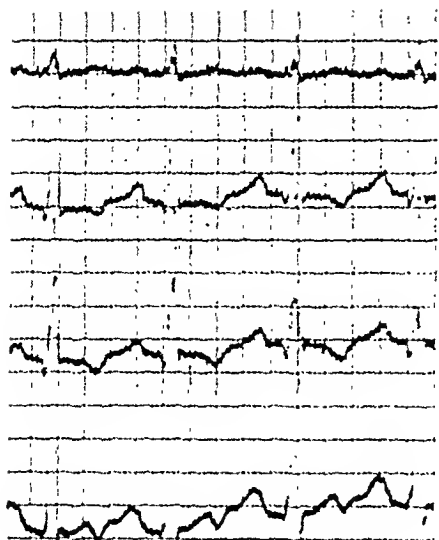
ECG 11 a.

Case 6. Soldier, aged 20 years. *Diseased heart.* Non-smoker. ECG 11 a: Hypoxia test without smoking. ECG after 6 minutes' hypoxia. Heart rate 120 beats per minute. T-waves deeply negative in leads II, III and CR.

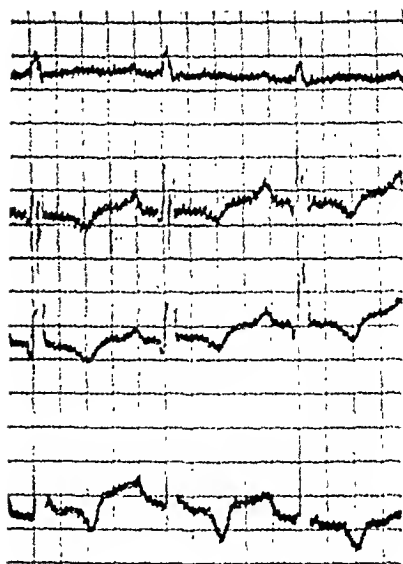
ECG 11 b: ECG after 17 minutes' hypoxia without smoking. Heart rate 120 beats per minute. T-waves somewhat more deeply negative.



ECG 11 b.



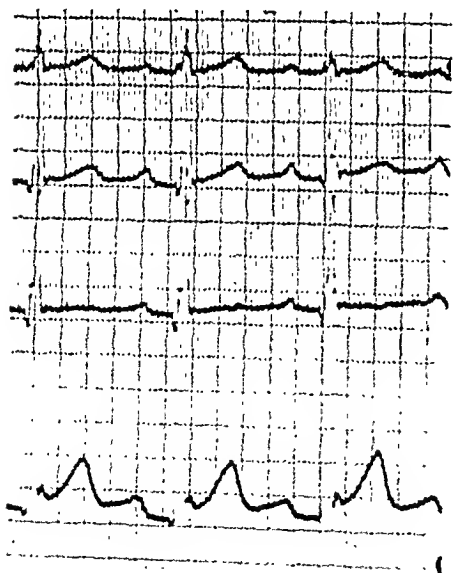
ECG 12 a.



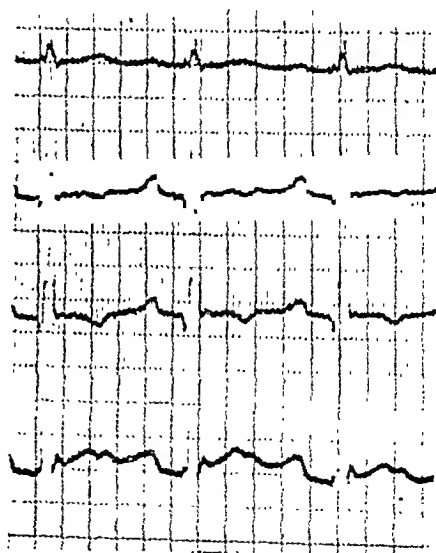
ECG 12 b.

Case 6. ECG 12 a: ECG after 6 minutes' hypoxia. Heart rate 133 beats per minute. T-waves negative in leads II, III and CR, as in the preceding test.

ECG 12 b: ECG after 17 minutes' hypoxia and after smoking cigar. Heart rate 130 beats per minute. T-waves somewhat more deeply negative (particularly in lead CR,) as in the control test.



ECG 13 a.



ECG 13 b.

Case 6. ECG 13 a: ECG 20 minutes after intravenous injection of 0.5 mg dihydroergotamin and after 6 minutes' hypoxia prior to smoking. Heart rate 106 beats per minute. T-waves now positive in leads I, II and CR.

ECG 13 b: ECG after 17 minutes' hypoxia and after smoking cigar. Heart rate 111 beats per minute. The T-waves have now once again been changed pathologically: slight negative in lead II, negative in lead III and deformed and markedly flattened in lead CR.

Discussion.

It appears from the investigation that tobacco smoking and injection of nicotine during hypoxia give rise to flattening, in isolated cases to inversion, of the T-waves. Simultaneously, an increase in the heart rate of approximately the same extent (10—20 beats per minute) as occurs during smoking under ordinary conditions with normal oxygen saturation, takes place.

It is striking that the ECG changes provoked by tobacco are most marked in the younger age group (group I). In the older age group (group II), the changes in the heart rate and in the T-waves are insignificant. One single exceptional case was, however, found: in case 5, cigar smoking produced «pathological ECG changes. The test was repeated 3 times with similar results.

How must the ECG changes observed be interpreted?
Tobacco smoking may be assumed to cause:

1. Decreased coronary circulation via constriction or spasm of the coronary vessels (the old classical hypothesis).
2. Increased secretion of adrenalin from the suprarenal glands and from the heart itself.
3. Hypopotassaemia.
4. Changed position of the heart during the hypoxia test as a sequel of the changed respiratory conditions.
5. Increased sympathetic tone.

1. It is, of course, impossible to draw any conclusions concerning the coronary circulation from the electrocardiographic observations made here. If the ECG changes were of coronary origin, they should have been more pronounced in the older age group, with naturally greater «physiological» changes in the coronary vessels due to age (25) than in the younger age group. The converse is the case. In one isolated case, case 5 (ECGs 9 a and 9 b), coronary origin is at least debatable. Another explanation is, however, just as probable (see below under 5): Investigations in animal experiments concerning the effect of nicotine on the coronary circulation have rendered contradictory results. Dietrich and Schimmer (22) found, however, in experiments on dogs with thermostromuhr that tobacco smoke and nicotine caused both reduction and increase in the coronary circulation. An increase was seen in all the experimental animals and a decrease, in addition, in half of the animals. The effect of nicotine could be abolished by means of atropine and potentiated by means of prostigmin. Not until strongly toxic or lethal doses of nicotine were administered in rabbits were electrocardiographic signs of myocardial anoxia produced: high, pointed T-waves of the type «Erstickungs-T» (26). Abnormally high, pointed T-waves were observed in acute nicotine poisoning in man (28). I myself, have seen 2 cases of paroxysmal auricular fibrillation in acute nicotine poisoning in 2 males with clinically healthy hearts, where the presence of myocardial anoxia was debatable (27, 28).

A priori, it is improbable that the changes in the T-waves observed here are of coronary origin.

2. Nicotine stimulates the suprarenal glands to increased secretion of adrenalin. The oxygen requirement of the heart is increased by nearly half when stimulated by such small quantities as 1—2 γ of adrenalin. The oxygen consumption is increased by 3 $\frac{1}{2}$ times with 10 γ adrenalin. Adrenalin increases the work of the heart considerably but increases simultaneously the coronary circulation and oxygen supply. This, however, does not nearly correspond to the sudden increase in oxygen consumption (Gollwitzer-Meier, 29). Adrenalin is not only produced by the suprarenal glands but also by the sympathetic neurons in the arterial walls and by the heart itself under the influence of sympathetic stimuli (30, 31, 32).

Thus, nicotine may by increased secretion of adrenalin exert a potent anoxiating effect on the myocardium. If, in addition, already from the commencement hypoxia is present in the heart, increased conditions for the development of coronary insufficiency are present. This might be the case at least in the older volunteers who reasonably must be assumed to have a lesser coronary reserve than have the younger volunteers.

3. It is known from animal experiments that injection of nicotine reduces the potassium content of the serum. This is also true in man (27). In one case of acute nicotine poisoning with alarming clinical symptoms in man, I myself observed a pathologically decreased value of the serum potassium (10.6 mg % (28)). It is, however, scarcely credible that the small doses of nicotine which are absorbed on tobacco smoking should give rise to any appreciable shift in the electrolyte balance and influence the ECG.

4. During the hypoxia test significant hyperventilation most frequently occurs which, however, becomes constant after the first 5 minutes. The hyperventilation produces greater or lesser variations in the position of the diaphragm with consequent changes in the position of the heart. Larsen (33) investigated the position of the heart at rest on deep inspiration and during hypoxia in some cases. He found, that an alteration in the position of the heart may be assumed to contribute to a slight degree to the development of changes in lead I and most frequently to counteract the development of changes in lead III. In my Case No. 1, I found that the position of the electric axis was practically unchanged in the ECG after 6 minutes' (angle $\alpha = +54^\circ$) and after 17 minutes' hypoxia (angle $\alpha = +52^\circ$) respectively.

Only in exceptional cases, on smoking during hypoxia, does a noticeable slight increase in hyperventilation occur.

5. According to Langley and Dickinson (34) the most important property of nicotine is, after a short stage of stimulation, to inhibit the ganglions of the vegetative nervous system, both parasympathetic and sympathetic. On a basis of animal experiments and electrocardiographic studies (1, 2), one is justified in maintaining that injection of nicotine and smoking of tobacco produces a shift of the vegetative tone of the heart in a sympatheticotonic direction. To support this it may be mentioned that the ECG changes, developed on tobacco smoking, have the same appearance as in conditions with increased sympathetic tone: tachycardia, high P-waves, low or negative T-waves and depressed S—T inter-

vals. Nicotine can exert its effect on the tone of the vegetative nervous system partly directly and partly indirectly via increased secretion of adrenalin as in paragraph 2 above. The ECG changes provoked by tobacco could be eliminated entirely or partly by an alkaloid of ergot such as dihydroergotamine (DHE 45). (See ECGs Nos. 3 a, 3 b, 6 a and 6 b). According to Rothlin and Cerletti (35), the ergot alkaloids produce primarily active vagal tone released via the central nervous system. In this way an extra-cardiac change of the tonic position of the heart in a vagotonic direction develops. In addition, the alkaloids of ergot exert a peripheral, indirect sympatheticolytic effect. Both these circumstances may explain why the sympatheticonic effect of nicotine on the ECG is abolished or reduced under the influence of dihydroergotamine. In case 5, however, the development of ECG changes after cigar smoking could not be prevented despite the fact that the volunteer received 0.6 mg dihydroergotamine intramuscularly 30 minutes prior to the hypoxia test. In a new experiment, pathological ECG changes were produced in the same case by 4—5 minutes cigar smoking. Thereafter, 1 ml Hydergin (CCK 179) was injected intravenously without effect on the ECG changes. This is of course, per se, no proof that these ECG changes were of coronary origin. The dosage of the sympatheticolytic preparation employed may have been too low (36) or the sympatheticonic effect of nicotine too potent. In this case, an experiment with inhalation of amyl nitrite according to Sjöstrand (37) was also performed. Although the heart rate increased following amyl nitrite as much as in one of the smoking tests, the ECG changes observed there could not be reproduced. In this case, cigar smoking produced an electrocardiographic coronary insufficiency. The question therefore arises whether a clinical (actual) coronary insufficiency was present in this case. The result of the amyl nitrite test favours this. The ECG changes, however, are much more reminiscent of those which occur on arterial orthostatic anaemia in an individual in the upright position than of those in clinical coronary insufficiency (Sjöstrand: personal communication). The most probable cause of the ECG changes after smoking in this case is excessive secretion of adrenalin. There are reasons for assuming that this very volunteer was particularly sensitive to nicotine.

Case 6, also, deserves further mention. This case was a soldier, aged 20 years, with *cardiac disease* without subjective cardiac symptoms and who had been assigned to full duty. The control test showed a pathological ECG after 6 and 17 minutes' hypoxia respectively (ECG Nos. 11 a and 11 b). ECG after 6 minutes' hypoxia was completely normalized by preliminary treatment with 0.5 mg dihydroergotamine intravenously (ECG 13 a). It is now a well-known fact that the alkaloids of ergot in some cases may be able to normalize ECG changes also of organic origin (36). Following cigar smoking, the T-waves became negative again in leads II and III and markedly flattened in CR₁. The effect of nicotine was in this case more potent than the vagotonic or sympatheticolytic effects respectively of dihydroergotamine.

Recently, it has been revealed that a definite relation exists between the rate of the heart and the amplitude of the T-waves. Sjöstrand (37) showed that the

T-waves decrease physiologically linearly in height with increased rate of the heart. The S—T interval also is depressed physiologically with increased rate of the heart. A depression of the S—T interval of up to 3—4 mm may occur in individuals with healthy hearts. Björkman (38) arrived at a similar result in his comparative investigation of the relation between the heart rate and the amplitude of the T-waves. He showed, in addition, that with increased rate of the heart the P-waves increased physiologically in height simultaneously with the flattening of the T-waves.

The acute oxygen deficiency during the hypoxia test releases a sympathetico-tonic reaction (36, 39), which gives rise to an increase in the heart rate and a flattening of the T-waves. On administration of tobacco smoke or nicotine the heart rate increases even more and the T-waves decrease further in height. The hypoxia tests without smoking (control tests) show, however, that normally, in the majority of cases, a continuous flattening of the T-waves develops, least in lead I and greatest in lead CR₁, during the course of the test. This occurs although the heart rate and oxygen saturation only show very small variations from the 6th to the 19th minutes of the test. This »physiological» flattening of the T-waves which probably is a sequel of a number of unknown factors is, in some of the cases, considerable (see Fig. 1). As a collective name of these unknown factors I have introduced the term »time-factor». This »time-factor» influences the T-waves in the majority of cases so that they diminish and in some few cases so that they increase, also during the smoking test, and must be eliminated before the effect of smoking alone on the T-waves can be calculated. The »time-factor» may numerically be defined as the difference in height between the T-waves as measured at 17—18 minutes' hypoxia and at 6—7 minutes' hypoxia. From Figure 1 the extent and direction of the »time-factor» appears. The »time-factor» was calculated from the control tests after correction of the individual values of the T-waves with regard to the individual changes concerning the heart rate. Lines of regression were calculated for all groups and tests. In doing this, the frequency was introduced as explicit variable and the T-waves as dependent variables. With the help of the regression coefficients (Table 1) adjusting standards were introduced to eliminate the effect on the T-waves which was caused by changes in the heart rate.

Table 1.

	Group I		Group II
	Smokers	Non-smokers	
T ₁	0.025	0.015	0.030
T ₂	0.050	0.025	0.050
T ₃	0.135	0.090	0.150

The above table indicates the extent of depression (in mm) of the T-waves which was caused by an increase in the heart rate by one beat per minute, or that increase in height of the T-waves which occurred on reduction of the heart rate by one beat per minute. The difference between the heart rates at the 17—

18 minutes' tests and at the 6—7 minutes' tests were calculated. These differences were later multiplied by the respective regression coefficients in the Table above. The factors obtained were later added to or subtracted from the heights of the T-waves in the 17—18 minutes' tests. After the heights of the T-waves according to the above principles were adjusted regarding the «time-factor» and differences in heart rates, the differences in heights between the T-waves on 17—18 minutes' hypoxia (after smoking) and on 6—7 minutes' hypoxia (before smoking) were calculated. These differences, when present, probably represent the effect of smoking. The differences between the heights of the T-waves before and after smoking appear from Table 2, below.

Table 2.

Differences between the heights of the T-waves before and after smoking following adjustment regarding «time-factor» and heart rate.

Group	I		II
	Smokers	Non-smokers	
<i>Mean values</i>			
T ₁	0.005	— 0.10	— 0.02
T ₂	0.02	— 0.21	0.41
T ₄	0.47	0.76	0.02
<i>Standard deviation</i>			
T ₁	0.4	0.6	0.3
T ₂	0.7	0.7	0.5
T ₄	1.7	1.6	2.4
<i>Mean error (under null hypothesis)</i>			
T ₁	0.08	0.16	0.09
T ₂	0.16	0.18	0.17
T ₄	0.38	0.47	0.66

It appears from the table that the effect of smoking on the T-waves is not significant in any of the groups.

The same condition is demonstrated graphically in a comparison of the lines of regression of the T-waves before and after smoking. The «time-factor» has been eliminated.

Group I: Smokers.

It is seen here that the lines of regression for T₁ and T₂ coincide completely while those for T₄ form a small angle.

Group I: Non-smokers.

Here also the lines of regression for T₁ and T₂ practically coincide. As regards T₄, the lines form a somewhat larger angle than in smokers.

Group II.

The lines of regression for T₁ practically coincide; for T₂ they form a small angle while for T₄ they form a considerable angle.

The angle between the lines in the various groups is probably not an effect of smoking but is attributable to the smallness of the material accounted for. With heart rates in the region of 110—120 beats per minute, one isolated and *extremely* high value of the T-wave occurs just in lead CR₄ in Fig. 4 which causes

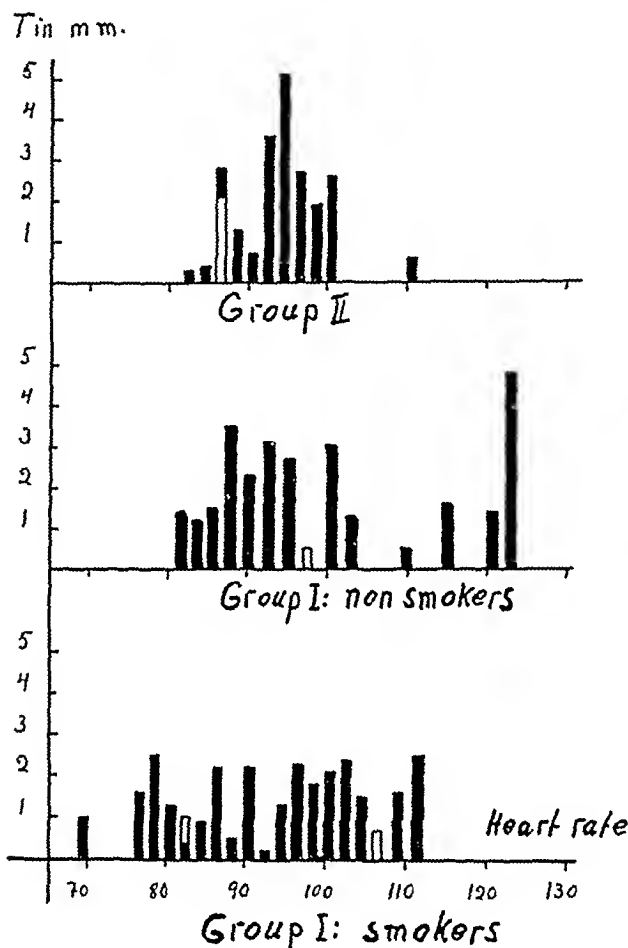


Fig. 1. The figure demonstrates the extent of the «time-factor» (in mm) in lead CR₄ in the various groups. Group I: smokers and non-smokers in the age group 20—26 years. Group II: volunteers in the age group 38—51 years. The black columns indicate that the «time-factor» influences the T-waves in a depressant direction and the white columns indicate an influence in a raising direction.

a marked rise of the interrupted line. If this value be excluded, the lines will take a practically parallel course.

It appears from Figure 1 that the «time-factor» is relatively small throughout in the smokers (group I) in 2 cases it is relatively large in non-smokers and in 2 cases (both non-smokers) it is considerable in the older age group (group II). Particularly in case 5, who reacted with a «pathological» ECG after smoking, the «time-factor» is considerable. It seems as if in the younger age group the non-smokers react more markedly to the prolonged hypoxia than do the

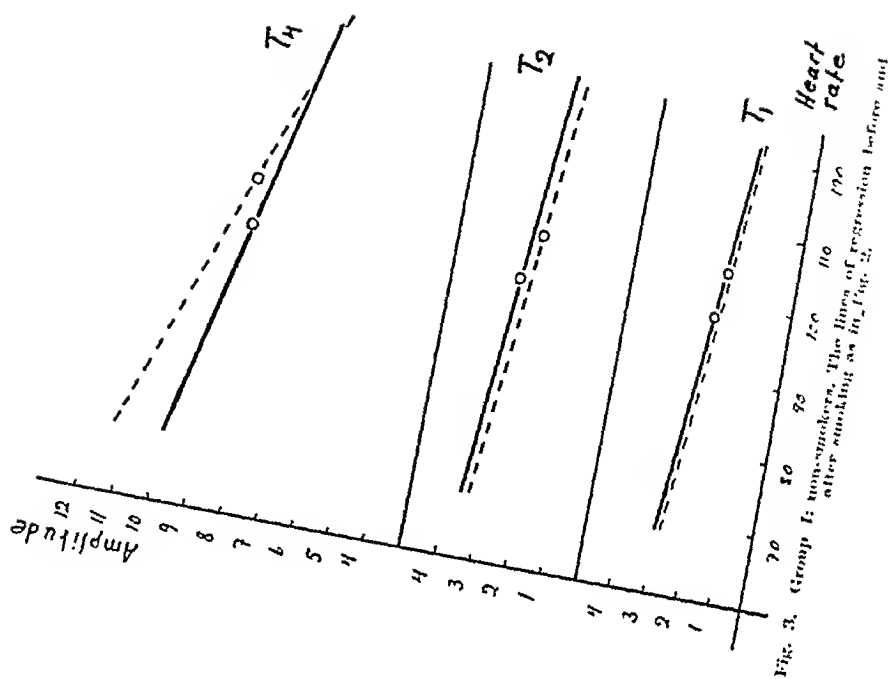


Fig. 3. Group I: non-smokers. The lines of regression before and after smoking as in Fig. 2.

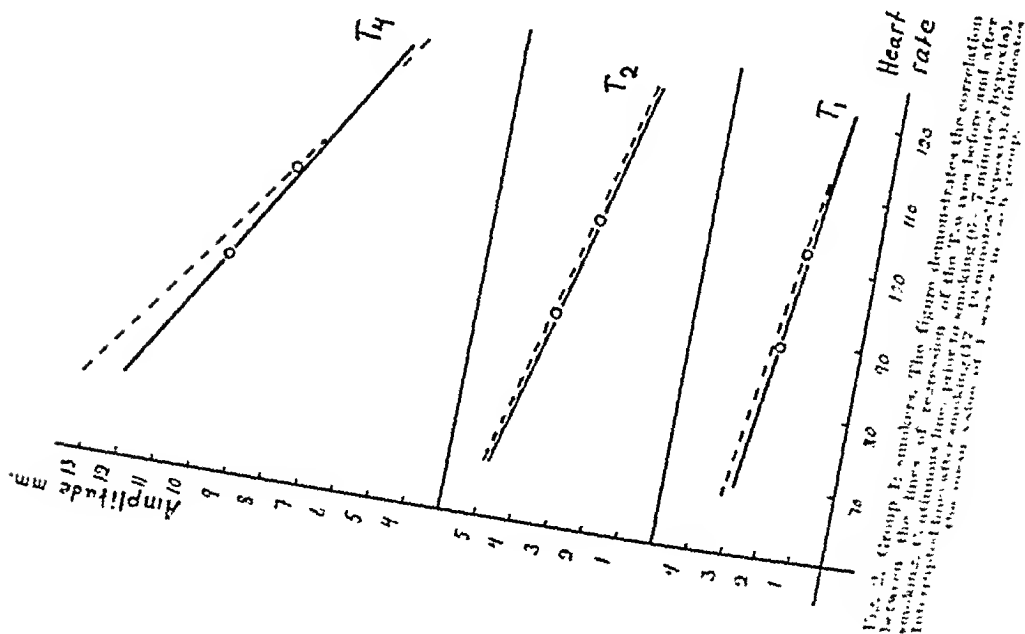


Fig. 2. Group I: smokers. The figure demonstrates the correlation between the lines of regression of the T_2 group before and after smoking, the continuous line, prior to smoking (0-7 minutes' hypoxia), and the dashed line after smoking (7-14 minutes' hypoxia). It indicates the mean values of 7 weeks in each group.

smokers. An acceptable explanation of this may be that the smokers on account of daily inhalation of small quantities of carbon monoxide in tobacco smoke have become accustomed to a certain, although slight, degree of hypoxia. In habitual smokers, as a rule, a content of 5–8 % carboxyhaemo-

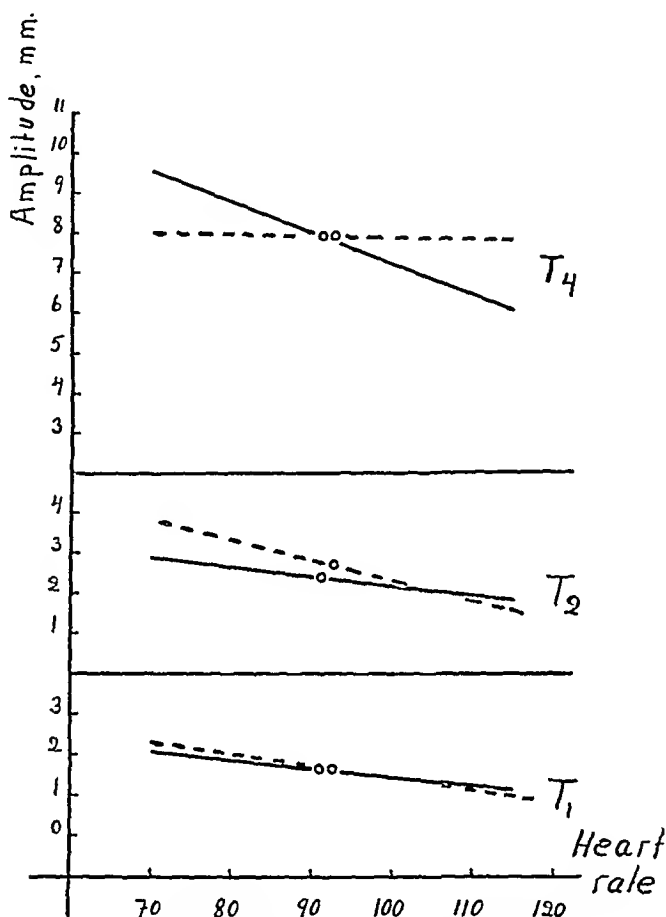


Fig. 4. Group II: Lines of regression before and after smoking. See text p. 117.

globin in the blood is found. Smokers have thus constantly slight hypoxia. The two volunteers in group II who reacted during the control test with a particularly marked flattening of T_4 (large «time-factor»), were both non-smokers. One of the cases (case 5) was 38 years and the other 50 years. It seems natural to assume that a coronary component is included in the «time-factor». This should make itself more marked in the older volunteers with naturally greater physiological changes in the coronary vessels due to age, than in the younger volunteers.

A collected and expanded material, comprising also the nicotine tests, will be published later in a more comprehensive work.

Summary and Conclusions.

The author investigated the effect on the ECG of tobacco smoking and nicotine during hypoxia.

The volunteers consisted of males with clinically healthy hearts in the age group 20—26 years (group I) and 38—51 years (group II) respectively. Group I consisted of 20 smokers and 14 non-smokers, group II of 10 smokers and 2 non-smokers.

After 6 minutes' hypoxia, when oxygen saturation, heart rate and respiratory rate were stabilized at constant levels, tobacco smoke was administered via a special lateral mouthpiece for 8 minutes. The test was concluded after 19—20 minutes' hypoxia.

1. The investigation shows that a linear correlation exists between the height of the T-waves and the simultaneously occurring increase in the heart rate on smoking.

2. The T-waves are thus not depressed in height on smoking more than would correspond to a similar increase in heart rate under physiological conditions.

3. Hypoxia as such does not accentuate the effect of tobacco upon the ECG except in isolated cases. In one case, a 38-year-old smoker, with a healthy heart, smoking produced »pathological» changes in the S—T intervals and T-wave (electrocardiographic coronary insufficiency).

4. The effect of nicotine can entirely or partly be eliminated by means of dihydroergotamine (DHE 45).

5. Tobacco smoking during hypoxia has thus, as a rule, no significant effect on the ECG.

References.

1. v. Ahn, B. E.: Svenska Läkartidningen No. 50, 3109, 1946. — 2. v. Ahn, B. E.: Ibid. No. 14, 785, 1947. — 3. v. Ahn, B. E.: Nord. Med. 41, 451, 1949. — 4. Evans, W. F. and H. J. Stewart: Am. Heart J. 26, 78, 1943. — 5. Graybiel, A., R. S. Starr and P. D. White: Am. Heart J. 15, 89, 1938. — 6. Levy, R. L., J. A. L. Mathers, A. A. Mueller and J. L. Nickerson: J. A. M. A. 135, 417, 1947. — 7. Reimell, H. and R. Winterer: Zschr. f. klin. Med. 141, 228, 1942. — 8. Segal, H. L.: Am. J. Med. Sc. 196, 851, 1938. — 9. Ssalischtscheff, A. and J. Tschernogoroff: Zschr. f. d. ges. exp. Med. 74, 193, 1931. — 10. Boyle, M. N., R. Wegria, R. T. Cathcart, J. L. Nickerson and R. L. Levy: Am. Heart J. 34, 65, 1947. — 11. Wegria, R., M. Segers, R. P. Keating and H. P. Ward: Am. Heart J. 38, 90, 1949. — 12. Morawitz, P. and A. Zahn: Dt-sch. Arch. f. klin. Med. 176, 361, 1944. — 13. Wilson, F. N. and F. D. Johnston: Tr. A. Am. Physicians 54, 210, 1939, and Am. Heart J. 22, 64, 1941. — 14. Bryant, J. M. and J. E. Wood: Am. Heart J. 34, 20, 1947. — 15. v. Ahn, B. E. and O. Göhle: Am. Heart J. 38, 775, 1949. — 16. v. Ahn, B. E.: A Case of Tobacco Angina. To be published. — 17. Auld, H. S., L. Pordy, K. Chesky and A. M. Master: Exp. Med. and Surg. 9, 248, 1951. — 18. Moschini-Antinori, E. and P. Solinas: Folia Cardiologica 10/4, 261, 1951. — 19. Pölet, S., A. Kershbaum, R. H. Meade and L. Schwartz: Am. J. Med. Sc. 201, 40, 1941. — 20. Katz: Cit. Jervell, O. and L. Eitinger: Nord. Med. 43, 160, 1950. — 21. Spillner, R., E. Corday, H. C. Bergman and M. Printzmetal: Cardiologia 21, 255, 1952. — 22. Dietrich, S. and G. Schimert jr.: Zschr. f. klin. Med. 135, 718, 1939. — 23. Jönvall, J.

- H. P.: *Acta Med. Scand.* *94*, 467, 1938. — 24. Malmström, G.: *Acta Med. Scand. Suppl.* *195*, 1947. — 25. Moon, H. D. and J. F. Rinehart: *Circulation* *6/4*, 481, 1952. — 26. v. Ahn, B. E.: *Cardiologia* *20*, 289, 1952. — 27. v. Ahn, B. E.: *Ibid.* *21*, 765, 1952. — 28. v. Ahn, B. E.: *Acta Med. Scand.* *145*, 20, 1953. — 29. Gollwitzer-Meier, Kl.: *Klin. Wschr.* *18*, 225, 1939. — 30. Raab, W.: *J. Clin. Endocrin.* *1*, 977, 1941. — 31. Raab, W. and A. B. Soule: *Am. J. Roentgenol.* *51*, 364, 1944. — 32. v. Euler, U. S.: *Cardiologia* *21*, 252, 1952. — 33. Larsen, K. H.: *Om forandringer i ekg hos sunde og syge under experimentel iltmangel.* Copenhagen 1938. — 34. Langley, J. N. and W. L. Dickinson: *Proc. Roy. Soc.* *46*, 423, 1889 and *J. Physiol.* *11*, 265, 1890. — 35. Rothlin, E. and A. Cerletti: *Helv. Med. Acta* *17*, 3, 1950. — 36. Kiss, A. and L. Slapak: *Wien. Zschr. f. inn. Med.* *4*, 162, 1951. — 37. Sjöstrand, T.: *Acta Med. Scand.* *138*, 191, 1950. — 38. Björkman, A.: *Acta Med. Scand. Suppl.* *255*, 1951. — 39. Cerletti, A. and A. Kallenberg: *Helv. Physiol. Acta* *6*, 795, 1948.
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Heart Failure in Chronic Pulmonary Disease.

By

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Introduction.

Until recently, heart disease secondary to chronic lung disease was generally attributed to mechanical factors. The elimination of a fairly extensive part of the pulmonary vascular bed was considered to be of prime importance (Sylla, Bernard and Kreis, Spain). The raised pressure in the pulmonary circulation which resulted from the vascular pathology was believed to be the determining factor in the development of cor pulmonale (Rubin, Willius).

Most authors suggested that emphysema and fibrosis of the lungs were the main etiological agents in the development of this condition. Mc. Michael and co-workers and Cournand with the Columbia-University group challenged this mechanical point of view. They directed attention to the marked disturbances in gas exchange existing in emphysema among which the low arterial blood oxygen saturation is of outstanding importance.

As to the mechanism of the development of the heart failure: the hypoxemia is supposed, firstly to increase the cardiac output thus satisfying the tissue need for oxygen, and further to burden the heart by the resulting secondary hypervolemia and polycythemia. A third factor is the direct unfavourable influence of the anoxia on the heart muscle. Moreover, breathing of gases with a low oxygen content has a direct immediate constricting influence on the pulmonary vessels directly (v. Euler c. s., Motley c. s.) or after some lapse of time (Heemstra, Doyle, Wilson and Warren confirmed this effect). This all means an increased burden for the R. heart, partially due to secondary pressure rise in the pulmonary artery. Heemstra demonstrated that hypoxia has (at least partly) a local influence on the pulmonary circulation.

This functional view has the advantage of accommodating itself without any difficulties to observations, made by several authors, indicating that many cases of this form of heart failure belong to the category »high output failure» (Mc. Michael, Richards), a fact which would be difficult to explain if the cause of pulmonary hypertension were only mechanical.

Heart failure could of course develop much sooner if the resistance in the pulmonary circulation is increased for mechanical reasons.

This functional concept has since then been generally accepted and is in accordance with our experience.

In spite of an enormous advance in understanding of the condition, we still think this concept does not completely account for clinical experience. To clarify this a few of our own observations are presented following a few data on the situation in normal individuals.

Data on mean pulm. art. pressure in normal individuals.

Table I.

	Number of cases	Rest cm H ₂ O	Exercise cm H ₂ O
Hickam c. s.	7	15.5	17.5
Dexter c. s.	8	20	
Cournand	10	18	

A mean pressure of 25 cm water must be considered to be the upper limit of the normal. This value roughly corresponds to 25–30 mm Hg for the upper limit of systolic pulmonary artery pressure. Slight exercise gives only a slight rise of pressure (Hickam l. c.), meaning that the vascular reserve can take the increased cardiac output without increase in the pulmonary artery pressure. This holds good so long as the cardiac output does not increase to more than twice (Hickam) or thrice (Cournand) the normal value.

a) Mechanical Factors.

Intracardiac mechanical obstruction (pure pulmonary stenosis) shows conclusively how enormous changes in pressure may be the result of purely mechanical difficulties (van Buehem, Gotzche). In pulmonary diseases, however, mechanical factors (decrease in the area of the vascular bed) have a definite but only slight influence. Table II shows this clearly in cases of pneumonectomy where 50 % of the vascular bed has been removed.

Table II.

Pulm. Art. Pressure after pneumonectomy (simplified from Geelen):

	Age	Mean pressure cm H ₂ O Pre-operative			Post operative		
		Rest	Exercise	Oxygen	Rest	Exercise	Oxygen
Tuberculosis	28	(13) ¹ 23.2	(7) 23.2	(5) 21	(12) 24	(8) 31	(5) 22.5
Bronchial Ca	50	(12) 18.6	(12) 23.7	(5) 16.3	(12) 24.5	(6) 31.2	(6) 24.5
Bronchiectasis	30				(10) 23.5	(7) 36.5	(7) 21.1

¹ No. of cases in brackets.

After the pneumonectomy slight exercise appears to cause a slightly greater pressure rise than before the operation (statistically not significant); obviously

this can be explained by accepting the fact that the vascular reserves are already used up. So further increase of the cardiac output has to be brought about by increase of the systolic pressure.

The minor effect of loss of vascular bed is also apparent from the non-decisive pressure rise in most patients with an extensive fibrosis — due to a healed M. Besnier Boeck (Orie). Table III a and b.

Table III a.

Pulm. Art. Press. Mean. cm H₂O.

Fibrosis caused by M. Besnier-Boeck-Schaumann

	Rest	Art. ox. sat.	Resid. air/ tot. cap. × 100
W. de Ha.	22	94	—
Kl. Hu.	24	97	27
V. Re.	36	95.5	—
Pos.	23	95	—
Fo.	29	92.5	48
Br.	31	98.5	42
N. de Vr.	30	—	—
L. Fe.	42	96.5	40
M. Br.	25	97.5	44.5
de H. Bo.	14	—	—

Table III b.

Fibrosis caused by M. Besnier Boeck Schaumann.

Pulm. art. press. mean cm H ₂ O.	Art. ox. sat.	Resid. air/ tot. cap. × 100
27.6 (10)	96 (8)	33 (18)

Probably the same conclusions arise from recent studies in silicosis (Giraud, Bolt).

In occasional types of (interstitial?) pulmonary fibrosis there is a marked influence on the pulmonary circulation. These cases, however, in our opinion are rare and probably represent specific diseases.

b) Emphysema.

Though in agreement with the generally accepted idea that mechanical factors are not of major influence, we could not confirm the important rôle of emphysema.¹

In only 1 of our 10 patients was the pulm. art. pressure at rest moderately elevated, as is shown in the next table, and in this group no case of heart failure occurred. Table IV a and b.

¹ Without going into discussion of this rather complicated problem a short explanation is necessary. We consider as «pure» emphysema those cases of obstructive distension in which no spontaneous asthmatic attacks occur, where dyspnea is caused by exercise and where there are few or no complaints at rest. On fluoroscopy the diaphragma movements must be minimal, all the symptoms must be more or less stabilized. There is an indefinite transition to clearcut asthmatic emphysema to which these cases (apparently) belongs. Of course no other definite etiological factor (silicosis) may be demonstrable.

No bronchial infection may be present.

Table IV a.
Uncomplicated emphysema. No cor pulmonale.

	Age	Pulm. art. press.		Cm H ₂ O diff.	Residual air/total cap.	Vital capacity. 1 sec. value	Adrenalin 0.3 mg Subc.	Histamine 0.02 mg i. v.	Erythr.	Art. ox. sat.
		rest	exerc.							
Sch-Sch .. ♀	58	22	37	+15	53-64	869 (23 %)	—	—	—	81-82-84.5-87-88
F. Ko. .. ♂	50	33	49	+16	44	1,500 (36 %)	+10	-11	5.06	89-86-89.5-93
Strooth. . ♀	61	16	22.5	+ 6.5	41-41	2,750 (28 %)	+17	0		97
Ben. ♂	57	21	37	+16	47	2,390 (24 %)	+12	0	5.4	92-94.5-96-98
Slach. E. ♀	51	24	33	+ 9	63-62	1,465	+15	—		94.5-97
De Vri. . . ♂	37	20	31	+11	53	2,445 (37 %)	0	—	5.0	100 %
Ste. ♂	66				55	2,075	+ 7	-24		93 %
H. Wij. . . ♂	61	27 1/2	51	+23 1/2	56.6-54	1,120 (32 %)	0	—		64 1/2 %
J. Boll. . . ♂	56	14	24	+10	56	2,755 (26 %)	+25	-22		91 1/2 %
F. Holl. . . ♂	58	27	44	+17	53-55	1,980 (24 %)	+12	-21		92 %
Mean 10 cases	±55	23	36.5	+14	51.8 %	29 %	+10.8 %			88.9 %

Cases of (pure) pulm. emphysema in which no pulm. art. pressure was measured

Table IV b.

	Resid. Air/tot. cap.	Art. O ₂
1. ♂ Pet.	63	87 1/2
2. ♂ B. d. J.	53	89 1/2
3. ♂ v. d. W.	57	81
4. ♂ Dante.	61	62 1/2
5. ♂ Nienh.	45	97 1/2 (49 1/2 after infection)
6. ♂ Bli.	65	81 1/2
7. ♂ Bol.	51	91
8. ♂ Holl.	53-55	92
9. ♂ Wy.	56.6	64 1/2
10. ♂ Ekamp.	52	78
11. ♂ Bollh.	56	97 1/2
12. ♂ Mart.	60	95 1/2
13. ♂ Sch-Sch.	61	81
14. ♂ Ko.	41	86
15. ♂ Stro.	41	97
16. ♂ Ben.	47	90
17. ♂ Slach.	63	94 1/2
18. ♂ de Vri.	53	100
19. ♂ Ste.	55	93
19. 15 ♂ + 4 ♀	55 % (42)	87 % (45)

In each case the lowest (O₂) or highest (resid. air) value ever obtained is reported. Net air values were obtained simultaneously.
Number of determinations in brackets.

As neither definite pulmonary hypertension nor severe hypoxia were present in this group there must be some clear explanation for this obvious difference from the current observations. We think the explanation may be found in the scant attention that has been paid to the major influence of infection. For among cases of the same type, with a bronchial infection the situation is different.

c) Bronchial Infection.

By far the most marked increase in pressure was demonstrated in the group of diffuse bronchial infection with or without fibrosis and bronchiectasis; all cases of pulmonary heart disease with heart failure belonged to this group¹ (table V). The infections were usually of the chronic type due to hemophilic bacteria (Mulder 1937—1952), often with a super-imposed acute episode generally due to pneumococci.

Table V.

	Age	Pulm. art. press. Mean cm H ₂ O		Syst. mm. Hg	Vit. cap.			Art. ox. sat.		Resid. air/tot. cap.	Erythr. $\times 10^6$	Infection	Heart failure
		Rest. ¹	Exc. ²		1 sec. val.	Adren. 0.3 mg subc.	Hist. 0.02 mg	Initial	After treatment				
Knev. ♂	55	36.5			38%	+ 8	70%	76	—80—82—84	47 %	6.4	++	+
Kasp. ♂	42	31.5			26%	+14	—	60	—79.5—90	50.5%	6.5	++++	+
Kost. ♂	47	31			21%	—	—	70.5	90.5	—	6.0	++++	+
Boel-B. ... ♀	50	60		75/35	45%			70.5	84.5		4.6	++	+
		44		40/5	55%	0	—17%	75		56 %	5.3	++	+
Eng. ♂	54			20/4	38%	+10	—	73.5	96	51 %	5.7	++++	+
V. Vee ... ♂	52	30	38	30/10	19%	+13	—20%	82	—92	36 %	4.2 ³	++	+
Vr. Vee... ♀	47	52	66	110/40 ³		+ 6	—30%	65.5	—82—77—84—91—92	—	5	++	+

¹ After the actual failure was over.

² anemia.

³ in failure.

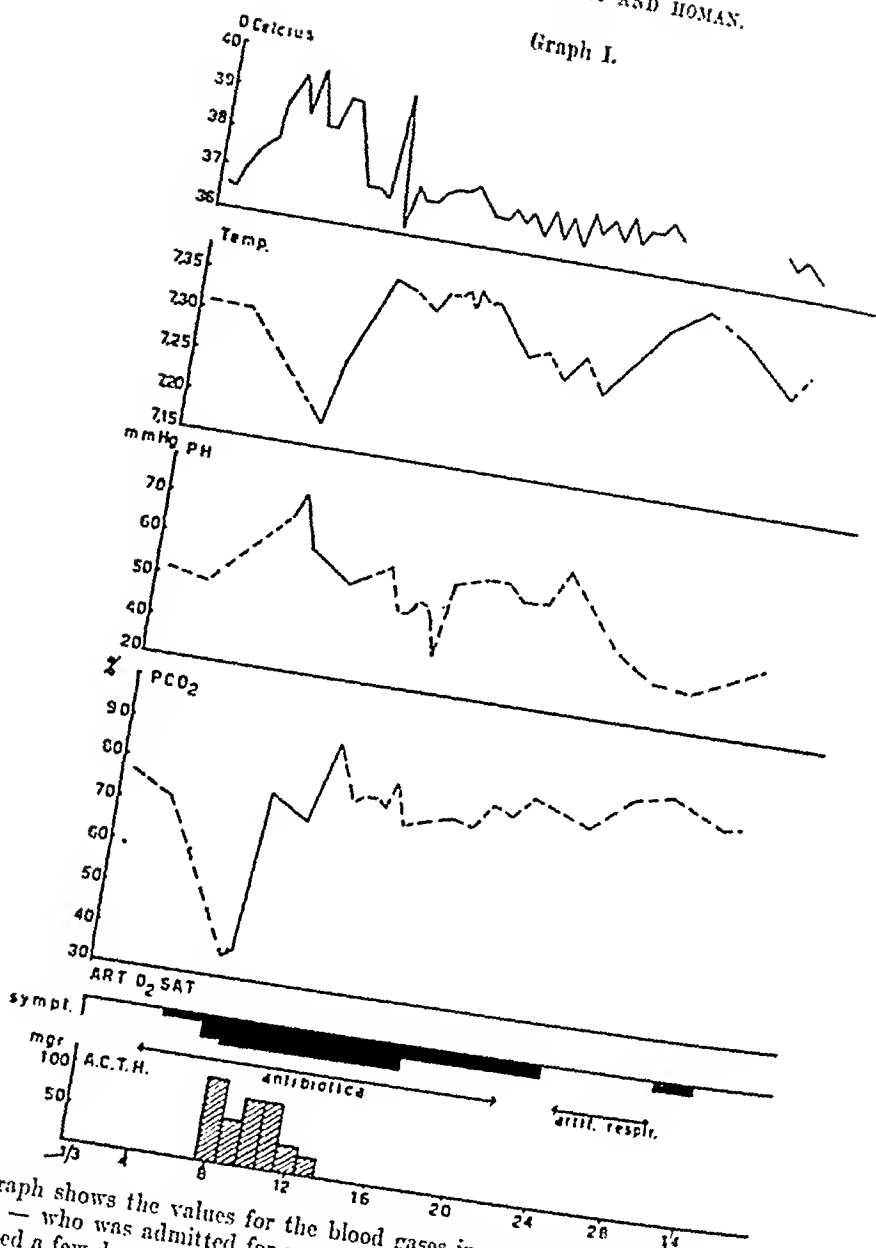
However, the residual air was only moderately increased; the grade of fibrosis was certainly not more severe than *e. g.* the diffuse fibrosis found in Morbus Besnier-Boeck-Schaumann or extensive tuberculosis, and the loss in the vascular bed was apparently not much greater than in pneumonectomy. When the asthmatic factors are predominant in these patients, the pulmonary artery pressure deviates more from normal as might be expected. Probably the main result of a bronchial infection is a sharp decrease of the arterial oxygen saturation as is shown in the accompanying graph (graph 1).

d) Hypoxia.

Ferrer as well as McMichael l. c. point out the influence of an arterial oxygen saturation below 82 % (80 %). In our experience also this limit seems to be of great

¹ Without going into details the prime importance of a correct diagnosis of bacterial bronchial infection may be stressed. The most important work done by Mulder in this field has until now received insufficient attention. (Mulder 1937—1952—1953) (Orie, 1952).

Graph I.



The graph shows the values for the blood gases in a patient with rather severe emphysema — who was admitted for pneumo-peritonium treatment. The bronchial infection started a few days after the admission in the clinic when only control blood samples had been taken.

importance. Firstly the anoxia directly effects an increase in the pulmonary artery pressure (Liljestrand l. c., Heemstra l. c.). Further an indirect rise in the pulmonary artery pressure was observed by Cournand (195 p. 651) together with a

increased amount of blood, polycythemia and increased cardiac output. It seems from our figures that without bronchial infection these low figures are not very often reached. Its rôle in producing R. heart failure has already been discussed.

Discussion.

If the bronchial infection is the trigger mechanism in starting heart failure, the often remarkably sudden onset of the latter is more easily understood. This also explains the fact that after the episode of failure (infection) is over, the situation is often not much different from that in cases with similar pulmonary disease in which no heart failure develops.

This fact originally stressed by Ferrer, is again pointed out by Mounsey. It explains the rarity of R. heart failure in cases in which only mechanical factors or minor hypoxia exist.

Table VI.

	Age aver- age	Pulm. art. pr. mean cm H ₂ O	Art. ox. sat.	Polycy- themia	Adrena- lin effect on vit. cap.	Resid. air	Bron- chial infection	Right heart failure
Normal ¹		20 (29)	94 %	absent	0	30 %	absent ?	0
Pulmonary stenosis	15	60 (25)	92 % (33)	absent	?	?	absent	0
Pneumonectomy		20.5 (10)	94 % (19)	absent	30 %	42 % (19)	0	0
Pure emphysema	55	23 (7)	87 %	5.1×10^6	80 %	55 %	absent	0
Emphysema + Infection	50	40	70 %	5.8×10^6	80 % (+)	49 %	+++	7

No. of cases in brackets.

¹ van Buchem l. c., Götsche l. c.

The pathological literature did not until now seem to support this view; recently published observations however are found to be fully concordant (Harri-son). In 132 cases of right heart failure (on 3,500 post mortems) hypertrophy of the right heart existed, 114 of them died of right heart failure; 109 showed chronic infections with or *without* emphysema.

Other Factors.

Yet there is no question that mechanical factors, emphysema and probably asthmatic factors contribute to the picture. If they are not present, severe arterial hypoxia or wide-spread bronchial infection seldom or never result in right heart failure. In pulmonary distention as well as in emphysema there is usually some

rise in pressure in the pulmonary circulation which may be due to loss in vascular area (table 1, table 4). In cases of more severe emphysema, hypoxemia resulting from disturbed intrapulmonary mixing is also a factor. The oxygen saturation at rest is shown in the table. However this factor may be accentuated by working conditions, in view of the fall in arterial oxygen saturation with exercise.

Probably another factor sometimes involved is the decrease in sensitivity of the respiratory centres to CO_2 in (longstanding severe?) emphysema. This factor in turn decreases the respiration and initiates a vicious circle resulting in more severe hypoxia (Donald and Christie). Asthmatic factors have without any doubt some influence. Lenègre and Zimmerman demonstrated that during an (artificially produced) asthmatic attack there was an increase of pressure in the lesser circulation (the reverse occurs after aminophyllin and epinephrin). Obviously the degree of irreversible damage involved in each case determines to a large extent the response to therapy and the reversibility of the condition.

In congenital heart disease and in some other conditions even an extremely low art. oxygen saturation never or only ultimately results in right heart failure. One could visualize that in the younger heart the increase in the coronary circulation may be so great that the oxygen shortage in the blood can be overcome (Hilton and Eichholtz). In older patients this increase in coronary flow apparently cannot be achieved. With vigorous young heart muscle and with long duration of the condition, the resistance of the right heart seems to be increased. The sudden onset of bronchial infections also means that a sudden load is put on the heart. This again may explain why heart failure more readily develops under these conditions. Besides it has to be kept in mind that also toxic substances from the bacterial infection may be important, but nothing specific is known in this respect.

It goes without saying that damage to the myocardium may also precipitate failure. When *cor pulmonale* develops without severe arterial anoxia we should also consider an anoxia of the heart muscle, resulting from a pre-existing coronary sclerosis with damaged heart muscle, as possibly the cause. A co-existing anemia may have the same effect. Some cases do exist in which (interstitial) fibrosis does provoke a very marked rise in pulm. art. pressure (100 cm H_2O). If in such a case heart failure develops (bronchial infection) it will often run a fatal course.

Doyle, Wilson and Warren attributed the particular vulnerability of individuals with cardiopulmonary abnormalities to hypoxia to two reasons:

1. They are unable to respond to local pulmonary disorders with effective local pulmonary arteriolar constriction.
2. They are unable to maintain oxygen transport to the tissues by increasing cardiac output.

They can neither maintain oxygen saturation by reducing the blood flow through airless or poorly aerated lung, nor compensate by increasing peripheral blood flow. Several important details of this statement will have to be proven and probably additional facts will be needed for complete explanation. But it is clear from all this, that imminent *cor pulmonale* can usually be recognised by a combination of anoxia and increased pulmonary pressure, and that infection plays a major part in the development of the actual failure.

The Electrocardiogram in Chronic Pulmonary Disease.

It is said that conclusive changes in the ECG and enlargement of the right heart which are expected to develop before the onset of increased venous pressure, edema, urobilinuria, liver enlargement often fail to appear or are very difficult to discern (v. Buchem l. c., v. Schoonhoven v. Beurden, Mounsey, Ritzmann, Selverstone). The subsequent electrocardiographic changes, based on the findings of Wilson, Goldberger, Meyers, White, and Kilpatrick, are:

1) No change or a deviation of the QRS-axis to the right, not exceeding the normal range of 110° according to Burch and Windsor. This may be due to the vertical position of the heart with a low diaphragm.

2) Right ventricular hypertrophy, with the following phases:

- a. abnormal right axis deviation in the limb leads.
- b. clockwise rotation.

These two symptoms can also be present without right ventricular hypertrophy in various cases, for instance by change of position of the heart in cases of pulmonary disease.

c. higher peaks of the right waves in the precordial leads over the right ventricle, often with depressed or inverted T. waves and prominent S. waves on the left ventricle and a marked P. pulmonale. It is superfluous to differentiate right ventricular strain from right ventricular hypertrophy, these concepts being for the greater part the same so that it is impossible to draw a borderline between them.

3) Incomplete or complete bundle block. Meyers considers a conduction delay of 0.03 tp 0.05 sec. in the intrinsic deflection as a feature of right ventricular hypertrophy.

4) Increase of the QRS-T angle as stated by Grant; a wide QRS-T angle can be due to an ischemic effect, or can be mechanical, due to changes in the systolic pressure of the ventricles.

In most cases these causes are indistinguishable.

5) A sign of heart failure apart from the above mentioned signs hypertrophy, axis deviation and bundle block may be an increase in the QT interval as a measure of a prolonged ventricular systole and a decrease of voltage.

We arranged our cases of chronic pulmonary disease into two groups, one in which right heart failure co-existed with, or preceded sputum infection (Table IV b case no. 1—7) and a second group in which emphysema was predominant (case no. 8—12). In case no. 8 with emphysema asthma was the main feature. In the first group we observed in six out of seven cases a marked deviation of the QRS-axis to the right, in the second group this occurred in only one patient, the one with the pronounced asthma. The angle between the QRS-axis and the T-axis was less than 45° in only one case of the first group (no 6) while in the second group it exceeded 45° only in the patient with asthma. The T-wave in the standard leads and the usual chest leads (V2, V4) was negative in four cases in the first group, and positive in all the other cases. In the chest leads a small Q was seen in only three cases, in V4, V6 together with a S-wave. It can be stated that in all

cases apart from case 10, where only lead V2 was made, a significant clockwise rotation was present.

If one considers the voltage of the QRS-waves in V2, V4 as one of the measures of right ventricular hypertrophy, no significant difference between the groups was found.

In five out of thirteen cases however the height of the QRS complexes averaged 20 mm. Right chest leads were taken in too few cases, therefore we can give no opinion on this. Courmand and co-workers pointed out its importance. Right ventricular hypertrophy in significant degree was seen by us in four cases of the first group. If clockwise rotation is considered as a sign of ventricular hypertrophy, this condition was seen in all cases. In none of our cases of uncompensated emphysema was there seen a marked deviation of the QRS-axis, though a kyphodiaphragm was present. The increase of the QRS-T angle was marked in some cases of the group with heart failure, and was normal in all the uncompensated emphysema cases.

Only in one case no. 8 was there seen a QRS-wave as long as 0.08 sec., in all the other cases it did not exceed 0.08 sec. In none of the cases did the Q-T interval exceed 0.4 sec. Courmand and co-workers also found it not to be lengthened. Summarising, it can be said that before the onset of heart failure in our cases clockwise rotation is present, this being the only electrocardiographic pattern. When failure is present a marked axis deviation and an increase in the QRS-T angle are seen, the other signs of hypertrophy being less constant. This is probably because the main factor causing failure need not be a long existing overburdening, may be a more or less suddenly arising increase of the load of the right heart, independently of the previous situation.

Therapy.

These considerations make it clear that intensive treatment of infection of the airways (the regulation of the arterial oxygen saturation being one of the results of this treatment) is of outstanding importance in cor pulmonale therapy. Other authors have already argued on similar lines. Direct oxygen therapy is another important measure. Care has to be taken that oxygen therapy does not result in depression of the ventilation as has been described and as we have observed repeatedly. In such cases additional measures have to be taken such as stimulation of the respiratory centre or artificial respiration. Therefore in cases of this type morphine is probably particularly hazardous often precipitating a fatal outcome. Cardiac stimulant drugs and diuretics will often be necessary to overcome the vicious circle, but sometimes rest in bed and anti-infective therapy alone are sufficient.

Phlebotomy is also advocated and probably often useful if there is an increase in total blood volume. However, in an anemia with normal blood volume, as sometimes occurs, cell transfusions are sometimes indicated and helpful.

Summary.

The influence of several factors in the development of right heart failure is discussed, with reference to cases of pneumonectomy (20 cases), M. Besnier Boeck (10 cases), pure pulmonary stenosis (13 cases), uncomplicated emphysema (20 cases) and emphysema of the lung complicated by infection (6 cases).

We are able to confirm that the influence of mechanical factors is only small (Cournand, Mc. Michael) and we have shown that this holds good also for the asthmatic factor and for emphysema. Anoxia resulting from uncomplicated, not infected lung diseases burdens the right heart, but only seldom to such a degree as to cause failure.

Failure is usually precipitated by a very marked fall in the arterial oxygen saturation (to far below 80 %) resulting from an infection of the deeper airways. Of course the first mentioned factors contribute to this condition and injury caused by the toxic influence of infection possibly also plays a rôle.

Where a damaged myocardium pre-existed, the situation is different, and probably the condition of the myocardium is partly determinative in the development of cor pulmonale.

The relations between these and other influences are discussed and suggestions are made regarding therapy. The electrocardiographic patterns are briefly mentioned.

References.

- Bernard, E., Kreis, B.: *Traité de Méd.*, Tome V, p. 618, Masson 1948. — Bolt: Personal communication. — Buehem, F. S. P. van, Nieveen, J., Homan, B., Verhey, J. B.: *Session Ned. Ziektek. Ver. Gent*, 26, 5, 1951. — Burch, G. E., Windsor, T. A.: *Primer of electrocardiography*. Lea and Febiger 1949. — Cournand, A.: *Circulation* 1950, 2, 641. — Cournand, A., Lequime, J., Regniers, P.: *L'insuffisance cardiaque chronique*, Paris 1952. — Dexter, L., Dow, J. W., Haynes, F. W., Whittenberger, J. L., Ferris, B. G., Goodale, W. T., Hellem, H. K.: *Journ. Clin. Invest.* 1950, 29, 602. — Donald, K. W., Christie, R. V.: *Clinical Science* 1949, 8, 33. — Doyle, J. T., Wilson, J. S., Estes, H. E., Warren, J. V.: *Journ. Clin. Invest.* 1951, 30, 345. — Euler, W. S. v., Liljestrand, G.: *Acta Phys. Sc.* 1946, 12, 301. — Ferrer, B. G., Goodale, W. T., Hellem, H. K.: *Journ. Clin. Invest.* 1950, 29, 602. — Geelen, E. E. M.: *Thesis, Groningen* 1953. — Giraud, G., Labour, H., Salvaing, J.: *Le poumon* VI, 505, 1950. — Goldberger, E.: *Am. Heart Journ.* 1948, 28, 621. — Unipolar lead electrocardiography, Lea and Febiger 1948. — Götzsche, H., Eskildsen, D., Tybjærg Hansen, A.: *Acta Med. Scand.* 1951, 139, 431. — Grant, R. P., Estes, H.: *Spatial Vector Electrocardiography*. The Blakiston Comp. 1951. — Harrison, C. V.: *Intern. Congress of Clin. Path.* London, July 1951. — Heemstra, H.: *Thesis, Groningen*, 1948. — Hickam, J. B., Cargill, W. H.: *Journ. Clin. Invest.* 1948. — Hilton, R., Eichholz, F.: *Journ. Phys.* 59, 413, 1934. — Kilpatrick: *Brit. Heart Journ.* 1951, 3, 309. — Lenègre, J. e. s.: *Le cœur des asthmatiques. Rapports du 2:e Congrès Internat. de l'asthme*, Expansion, Paris, 1950, 148, 210. — Mc. Michael, J.: *Edinb. Med. Journ.* 1948, 60, 65. — Meyers: *Am. Heart Journ.* 1948, 35, 1. — Motley, H. L., Cournand, A., Werkö, L., Himmelstein, A., Dresdale, D.: *Am. Journ. Phys.* 1947, 150, 315. — Mounsey, J. P. D., Ritzmann, L. W., Selverstone, N. J., Briscoe, W. A., Lemore, M. G. A. Me.: *Brit. Heart Journ.* 1952, 2, 153. — Mounsey, J. P. D., Ritzmann, L. W., Selverstone, N. J.: *Brit. Heart J.* 14, 442, 1952. — Mulder, J.: *Thesis, Groningen* 1937. — Mulder, J. et al.: *Acta Med. Sc.*

1952, 143, 32. — Mulder, J.: 3:ième Congrès international pour l'étude des bronches. Utrecht, June 5—6, 1953. — Orie, M. G. M.: Diseases of the chest 1952, 22, 107. — Orie, N. G. M., Wermeckerken, J. v., Buytendijk, H. J.: Session Ned. Ziektek. Ver. Utrecht 9, 4, 1949. — Richards, D. W. J.: Fed. Proc. 1945, 4, 215. — Rubin, E.: Diseases of the chest. Saunders 1947. — Schoonhoven van Beurden, A. J. R. S. v.: Ned. Tijdschr. v. Geneesk. 1951, 95, 1694. — Spain, M. D., Handler, B. J.: Arch. Int. Med. 1946, 77, 37. — Sylla, A.: Lungenkrankheiten, Urban und Schwarzenberg 1952, p. 68. — White, P. D.: Heart Disease. The Macmillan Comp. 1951. — Willius, U.: The chest and the heart. Thomans Springfield 1948, 1464. — Wilson, F., Rosenbaum, F., Johnson, F.: Advances in Int. Med. 1947, II, 63. — Zimmermann, H. A.: Diseases of the Chest 1951, XX, 46.

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Inulin Clearance Studies.

Concerning the Causes of the Reduced Clearance Figures in Successive Periods after One Injection of Inulin.

By

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(Submitted for publication August 18, 1953.)

It is still doubtful whether inulin clearance (Cl_I) is an exact expression of glomerular filtration. Various methods have been employed in an attempt to throw light on this problem. The methods most in use are simultaneous clearance tests with different substances and phlorizin tests. Ferguson and his associates (1950) have investigated Cl_I in human beings after one injection of this substance, and on the basis of their findings have come to the conclusion that some inulin is re-absorbed in the tubules, and that Cl_I is approximately 15 % lower than the glomerular filtration. At the Medical Department B. of the Rikshospital some years ago we have made observations similar to those of Ferguson and his associates, but we believe that other factors than a possible inulin re-absorption in the tubules must also be included in the discussion of the reasons why Cl_I shows falling figures from one period to another in clearance tests.

The determination of Cl_I after one injection of inulin marks a considerable simplification of the test in comparison with a permanent intravenous infusion, and a single injection of inulin for clearance tests has frequently been given in hospital. This method is discussed in Scandinavian publications by several writers (Josephson & Lindahl 1943, Hogeman 1943 and several others).

Procedure. In the fasting state and while the patient is confined to bed, inulin »Astra» is given as a single intravenous injection in a dose of 100 mg/kg body weight, the clearance tests being started one hour after the injection, and the patient having drunk one litre of water before the test was started. In the test series to be recorded here, Cl_I was determined in several successive periods of about 20 minutes' duration. Samples of blood were taken at the beginning and end of a period, and the mean inulin concentration in the periods was determined

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by recording the plasma inulin concentrations in a semi-logarithmic system and interpolating to 2 1/2 minutes before the mid-point of a period. The bladder was evacuated by a catheter and irrigated with saline solution. The inulin analyses were carried out according to a method described earlier by the author (Laake 1945). The Cl_I figures were corrected to a 1.73 m^2 body surface.

Own observations. Our normal material consisted of 9 patients (6 women and 3 men) on whom 12 clearance tests were carried out (Table I). In order to elimi-

Table I.
Inulin clearance after a single intravenous injection of it.
Normal material.

Pat. nr.	Period	P_I mg/100 ml	UV_I mg/min.	Cl_I ml/min.
1	1	13.5	1,842.8	136.5
	2	11.7	1,494.1	127.7
	3	10.1	1,247.4	123.5
	4	6.—	647.4	100.9
	5	3.9	374.4	96.—
1	1	15.75	2,318.4	147.2
	2	12.3	1,845.—	150.—
	3	11.2	1,496.3	133.6
	4	8.5	983.5	115.7
	5	6.9	716.9	103.9
2	1	19.5	2,275.4	116.7
	2	14.7	1,815.5	123.5
	3	9.9	1,079.1	109.—
	4	8.1	747.6	92.3
	5	5.6	469.8	83.9
2	1	20.5	2,406.7	117.4
	2	17.1	1,997.3	116.8
	3	10.3	1,108.3	107.6
	4	7.6	709.1	93.3
	5	5.3	502.4	94.8
3	1	24.—	3,655.2	152.3
	2	18.3	2,501.6	136.7
	3	9.1	1,313.1	144.3
	4	5.9	741.—	125.6
	5	3.1	317.8	102.5
4	1	11.—	1,227.6	111.6
	2	8.5	926.5	109.—
	3	5.8	589.3	101.6
	4	4.1	343.2	83.7
	5	3.5	263.6	75.3
5	1	13.—	1,545.7	118.9
	2	10.9	1,348.3	123.7
	3	6.3	707.5	112.3
	4	5.5	509.3	92.6
	5	4.3	427.—	99.3
5	1	18.—	2,098.8	116.6
	2	11.3	1,235.1	109.3
	3	7.2	826.6	114.8
	4	4.7	468.1	99.6
	5	3.6	314.3	87.3

Pat. nr.	Period	Pr mg/100 ml	UV _r mg/min.	Cl _r ml/min.
6	1	14.3	1,605.9	112.3
	2	10.1	1,117.1	110.6
	3	7.9	812.9	102.9
	4	5.5	490.6	89.2
	5	4.3	314.3	73.1
7	1	12.5	1,492.5	119.4
	2	9.7	1,198.—	123.5
	3	7.9	929.8	117.7
	4	6.4	655.4	102.4
	5	5.1	469.7	92.1
8	1	20.—	2,900.—	145.—
	2	15.3	1,941.6	126.9
	3	11.8	1,541.1	130.6
	4	8.9	1,017.3	114.3
	5	7.2	718.6	99.8
9	1	15.—	2,263.5	150.9
	2	10.8	1,550.9	143.6
	3	8.—	1,114.4	139.3
	4	5.8	746.5	128.7
	5	4.3	513.—	119.3

nate the influence of age on the clearance figures, the patients selected for this study were under the age of 30. Table I shows that the Cl_r figures have a falling tendency from the first to the fifth period, and that in the first and second periods they are almost identical with the figures given by other observers. By variance analysis (Bartlett's test for variances), a significant difference is to be found between the means of the periods (Table II). In order to ascertain how this reduction of the clearance figures behaves, it is necessary to compare the means for each period both by a one-way and a two-way classification. By the two-way classification the variations between both the periods and the patients are tested, and it is shown that *there is no significant difference in this material between the Cl_r figures in the first and second periods, whereas from the third period this difference is significant*. Further evidence in support of this observation is to be found by a study of the signs of the differences, and it thus becomes plain that *the fall in the clearance figures from the first to the third period is real*.

The reduction of the Cl_r figures through the series of tests can also be analysed

Table II.

Variance analysis of inulin clearance figures. Normal material.

	Periods				
	1	2	3	4	5
Cl _r ml/min.					
Mean, xj.	128.7	125.1	119.8	103.8	93.9
Variance, sj ²	240.9	158.1	188.3	197.4	151.5
Standard deviation, sj.	15.5	12.6	13.7	14.—	12.3

by regression studies. The regression of the Cl_I figures in relation to the periods (t) is a linear function (Fig. 1), and the regression coefficient 9.08 is significant.

When, as in the present material, a reduction of the Cl_I figures is demonstrable, and when there is a fall of the plasma-inulin concentration (P_I) the question may be raised whether it begins at a definite P_I reduction. If the reduction of the Cl_I figures was determined by a tubular re-absorption of inulin, we should

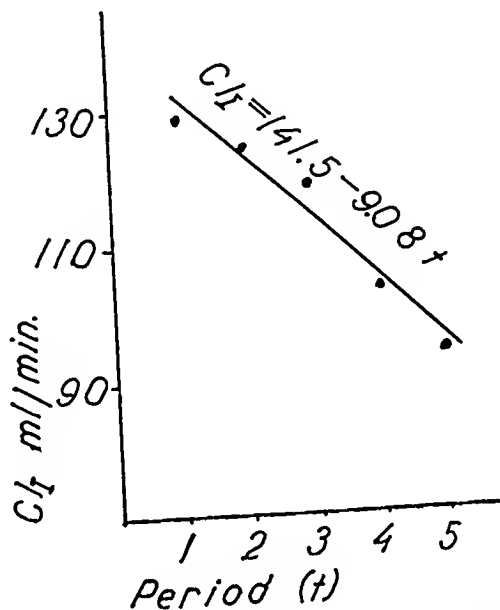


Fig. 1. Means for Cl_I in the periods 1—5. Normal material.

find it reflected in the regression of UV_I in relation to P_I . Table I shows that in several series of tests the Cl_I reduction begins when P_I is about 10 mg/100 ml. The regression lines for each clearance test are calculated, and a linear regression is found for the whole of the normal material. The regression is also calculated for all observations with $P_I > 10$ mg/100 ml. For the whole of the material the regression line is (Fig. 2):

$$UV_I = 145 P_I - 239.5.$$

And the regression line for the 26 observations in which P_I was > 10 mg/100 ml:

$$UV_I = 147 P_I - 276.8.$$

It will thus be seen that this last regression line is slightly steeper than the regression line for the whole of the material. *There is no evidence to show that the fall in the Cl_I figures occurs with any definite P_I .*

For the whole of the normal material the regression line does not pass through origo, but the departure from origo is not significant.

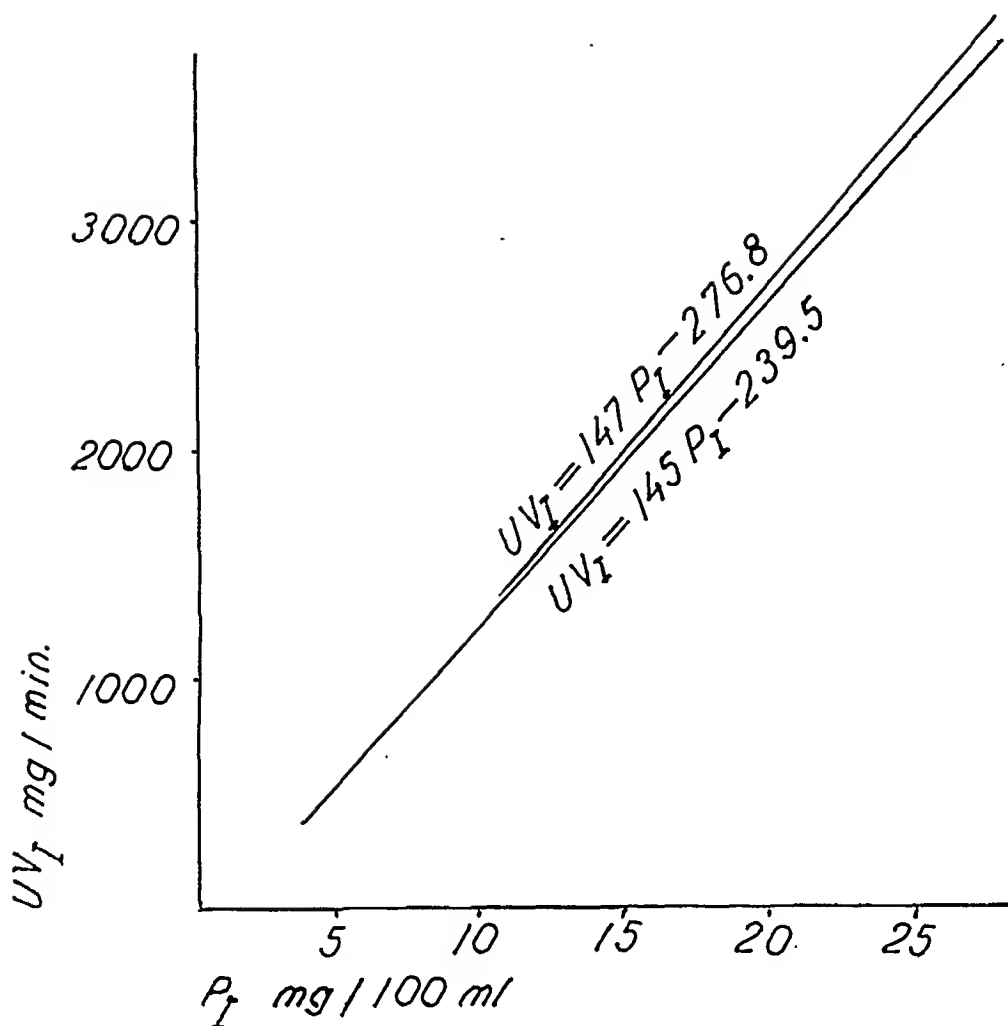


Fig. 2. The regression of UV_I with reference to P_I . Normal material.

A series of clearance tests with patients suffering from chronic nephritis, pyelonephritis and Boeck's nephritis also shows that Cl_I falls from the first to the fifth period (tables III & IV), but the difference between the means of the periods is hardly significant. In the present series of tests the number of observations is small and the variations are wide. On the classification analysis already referred to it was found that *the difference between the means of the periods was less marked in the subjects of renal disease than in a normal material*. In the normal material the difference was significant at the 1 % level, whereas this was not the case among the subjects of renal disease before the 5 % level was reached.

The regression of the Cl_I figures through the periods occurs according to the equation (Fig. 3):

$$Cl_I = 58 - 2.7 t$$

Table III.

Inulin clearance after a single intravenous injection of it. Cases of renal disease.

Pat. nr.	Period	P_I mg/100 ml	UV_I mg/min.	Cl_I ml/min.
1	1	24.—	1,814.4	75.6
	2	19.7	1,579.9	80.2
	3	16.3	1,155.7	70.9
	4	13.1	855.4	65.3
	5	10.9	599.5	55.—
2	1	15.5	1,100.5	71.—
	2	12.8	833.3	65.1
	3	10.2	759.5	74.5
	4	8.3	483.9	58.3
	5	7.1	459.4	64.7
3	1	24.—	1,449.6	60.4
	2	17.3	960.2	55.5
	3	13.6	697.7	51.3
	4	9.2	397.4	43.2
	5	6.7	302.2	45.1
4	1	25.—	1,140.—	45.6
	2	20.7	979.1	47.3
	3	16.1	644.—	40.—
	4	12.7	541.—	42.6
	5	11.2	444.6	39.7
5	1	22.5	1,496.3	66.5
	2	15.8	962.2	60.9
	3	11.2	719.—	61.2
	4	8.3	459.—	55.3
	5	6.5	332.8	51.2
6	1	24.8	1,031.7	41.6
	2	21.5	814.9	37.9
	3	17.2	689.7	40.1
	4	13.—	474.5	36.5
	5	10.2	346.8	34.—
7	1	18.9	780.6	41.3
	2	16.8	621.6	37.—
	3	14.7	595.4	40.5
	4	12.3	434.2	35.3
	5	11.4	387.6	34.—
8	1	22.5	767.5	35.—
	2	19.3	719.9	37.3
	3	16.9	518.8	30.7
	4	15.1	484.7	32.1
	5	14.6	459.9	31.5

The slope of the regression line differs from the normal material (Fig. 1). The regression coefficient is also significant in the material including patients suffering from renal disease. In this latter group the regression UV_I in relation to P_I is a linear function, and the line goes through origo (Fig. 4).

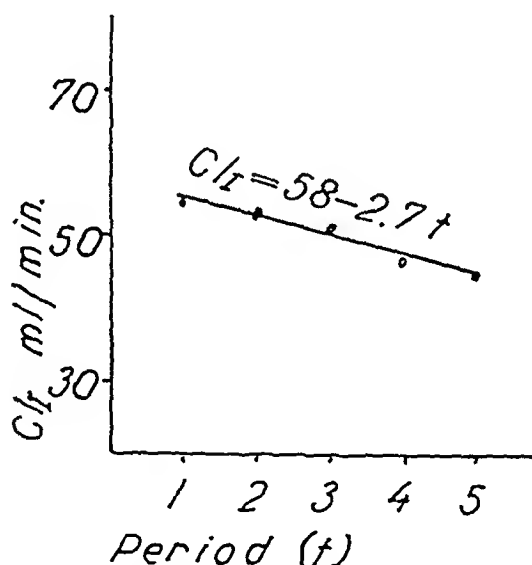
Table IV.

Variance analysis of inulin clearance figures. Cases of renal disease.

	Periods				
	1	2	3	4	5
Cl_i ml/min.					
Mean, \bar{x}_j	54.6	52.7	51.5	46.1	44.4
Variance, s_j^2	212.—	214.6	235.6	128.4	122.—
Standard deviation, s_j ...	14.6	14.7	15.3	11.3	11.—

Discussion.

Selhaechter and his associates (1950) have studied the distribution curve of inulin. After a single intravenous injection there is a rapid fall of P_i in human beings, and the inulin content of interstitial fluids rises. But after about 10 minutes the concentration of inulin in tissue fluids begins also to fall because the inulin diffuses back into the blood. About 55 minutes after the injection, the concentration of inulin in the plasma and tissue fluids is identical for a short

Fig. 3. Means for Cl_i in the periods 1—5. Cases of renal disease.

time, but later on the inulin content of the tissue fluids is higher than that of the plasma. An equal distribution of inulin in the organism is not effected after a single injection (Robson and his associates, 1950). Inulin spreads relatively slowly in the organism because of its low diffusion coefficient. This is particularly the case when the vascular supply of the tissues is scanty. Guadino & Levitt (1949) have shown by animal experiments that when a permanent intravenous infusion of inulin is given, it takes more than two hours before equilibrium is

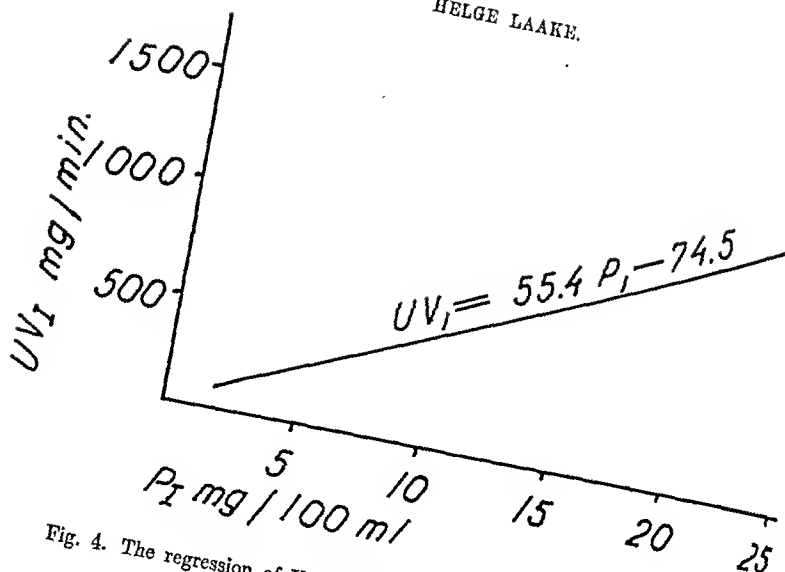


Fig. 4. The regression of UV_I with reference to P_I . Cases of renal disease.

established between plasma and extracellular fluid. Inulin is therefore little suited for the determination of extracellular space. The lack of equilibrium between plasma and tissue fluid means that there will be a concentration gradient for inulin between extracellular fluid and plasma. When Ferguson and his associates (1950) compared the Cl_I figures after a permanent and a single intravenous injection, they found that the mode of administration did not influence the reduction of the clearance figures in the successive periods.

The inulin analyses are carried out in venous blood. Arterial blood is filtered in the kidneys, and any arterio-venous concentration-difference for inulin which might occur would represent a source of error. The concentration of inulin in arterial and venous blood is almost identical and at any rate differences in this respect are so slight that they are of no practical importance. Ferguson and his associates have shown that the defective equilibrium in the organism in relation to inulin after a single intravenous injection of it does not play any part in the reduction of the clearance figures because the concentration difference in arterial and venous blood is so small.

A rapid fall of P_I in the test periods can be responsible for the reduction of the clearance figures as the correction to 2 1/2 minutes before the mid-point of a period under these conditions can give a too high P_I and therefore a reduction of the Cl_I figures. This source of error can, however, be of no practical importance when the plasma concentration falls relatively slowly as in our series of tests (Table I). Further, the fall of the concentration is relatively slower the further we advance in the periods. Our calculations also show that the reduction of Cl_I did not occur in connexion with any definite plasma concentration. McSwiney and his associates (1950) have shown that the delay time is fairly constant at 2.1 minutes (from 1.3 to 2.8), whereas it is put at 6 minutes by other observers:

(Brun and his associates (1949)). Both calculations of time for P_1 are employed by Ferguson and his associates, and it was noted that the course of the regression line was independent of the method of calculation employed.

With a falling P_1 there is a possibility that the analysis error may make itself more felt in the last clearance period, the clearance figures being influenced thereby. The method of inulin determination we have employed is accurate even when the plasma concentration is low, and the regularity with which the reduction of Cl_I occurs throughout the periods indicates that errors of analysis are not to blame. We must also take into account the stability of inulin and the possible presence of decomposition products (fructose). In order to check up on the stability of the preparation of inulin employed, we have used the procedure described by Josephson & Lindahl (1943), and like them we have found that inulin «Astra» satisfied the criteria necessary for a good inulin preparation.

In Smith's laboratories a sudden reduction of the diuresis has been shown to be accompanied by a transitory and apparently false reduction of the clearance figures, while conversely a sudden increase of diuresis has entailed a rise of the clearance figures. Smith is not able to give any satisfactory explanation of these observations. It has been assumed that variations in the delay time might be responsible, but McSwiney and his associates (1950) have shown that the delay time is independent of the diuresis. In the present material no sudden reduction of the diuresis has occurred from one period to another, so in our opinion we can exclude this causal factor as being responsible for a reduction of the clearance figures. It is probable that errors of analysis and errors in determining the volume of urine are also of minor importance in this connexion.

In the discussion of the causes of the reduction of the clearance figures in successive periods, much importance has been attached to changes in the glomerular haemodynamics. A reduction of the circulation of blood through the kidneys may entail a reduction of glomerular filtration, but a reduced circulation of blood through the kidneys does not necessarily reduce the quantity of the filtrate, Ekehorn (1944). Perfusion tests of anaesthetized dogs, — Shipley & Study (1951) have shown that even if the perfusion pressure varied between 80 and 180 mm Hg, the circulation of blood through the kidneys, the glomerular filtration, and the extraction of inulin expressed as a percentage remained relatively constant. We are not entitled to draw conclusions by analogy from experiments on animals, applying them to medical problems in man, but these tests have shown that glomerular filtration remains relatively constant under varying conditions. Prolonged clearance tests on human beings may constitute a stress which influences renal haemodynamics. In arranging our tests we have tried as best we could to eliminate emotional factors. Investigations (not yet published) of the circulation of blood through the kidneys at our hospital show that it is relatively constant with the method of testing we have employed. Our findings, compared with those of other observers, seem to indicate that the variations in the Cl_I figures can hardly depend on a reduction of the circulation of blood through the kidneys.

Anatomical investigations of the blood supply of mammals indicate the im-

probability of glomerular function being intermittent, and quantitative titration tests with glucose and diodrast — Smith (1943) show that in human beings an insignificant number of glomeruli ($< 5\%$) show an intermittent reduction of function. The variations in the Cl_i figures can hardly have any connexion with this intermittent function in a few nephrones as this function is never under 60 % of the mean function. Kruhoffer (1946) has shown by experiments that inulin is not deposited in the reticulo-endothelial system, and that it is also not excreted by the liver. Landowne & Alving (1947) have shown that inulin is not deposited in the human kidney. We may also ignore the possibility of extrarenal excretion and/or deposition of inulin as a cause of the reduction of the Cl_i .

In 1937 McCance & Widdowson showed that a shortage of salt in human beings entails a moderate reduction of renal function as measured by inulin, kreatinin and urea clearance. When the shortage of salt was again repaired, the clearance figures returned to normal. These authors discuss various possible causes of the reduction of the clearance figures, but they cannot give any convincing explanation of these observations. During a shortage of salt there is marked reduction of the extracellular fluid, and it is probably this which accounts for the reduction of the clearance figures. There is a reduction of the glomerular filtration in both man and beast during dehydration, and conversely there is an increase of glomerular filtration on expansion of the extracellular volume of fluid, — Smith (1951). The regulation of the volume and composition of extracellular fluid is sensitive. On water-tolerance tests there is a quick response, but conditions are restored to normal after about two hours. Black (1953) assumes the existence in the kidneys of a trigger mechanism with regard to the composition and distribution of extracellular fluid. Trueta and his associates (1947) have drawn attention to the importance for renal function of a constant fluid-balance in the organism, and they discuss changes in the intrarenal circulation resulting from a change of fluid balance. Moyer and his associates (1950) have confirmed Trueta's findings, whereas other investigators claim to have disproved them. We do not understand the mechanism governing the fluctuations of renal function in relation to the extracellular space, but it is conceivable that several factors such as hormonal and/or nervous factors are involved. It is possible that the juxta-glomerular apparatus occupies a central position in this system of regulation. In order to achieve constant experimental conditions during the clearance periods, it is essentially important to keep the extracellular volume constant. It is not likely that the variations in diuresis following variations in the extracellular space are responsible for the variations in the clearance figures.

The filtration pressure in the glomeruli is influenced by the intrarenal (interstitial) pressure, as the capsule pressure is identical with the intrarenal pressure which is relatively independent of the variations in the circulation of blood through the kidneys. But in connexion with water diuresis, the pressure can rise from 10 mm to 20—30 mm Hg. Smith (1943) found that the rise of the intrarenal pressure occurred from 90 to 150 minutes after the administration of fluid. The increased intrarenal pressure reduces the effective filtration pressure which in its turn influences the quantity of the filtrate. It is thus that the variations in

the intrarenal pressure can contribute to a reduction of the clearance figures, and the time at which this reduction occurs corresponds to the increase of the intrarenal pressure.

After a single intravenous injection of inulin, Landowne & Alving found a correlation of the inulin in urine inulin in plasma to be linear, the correlation line passing through origin when the plasma concentrations were between 0.5 and 3 mg/100 ml, provided that the extracellular volume of fluid was kept as constant as possible. These findings should indicate that there is no tubular re-absorption of inulin. By means of their regression analyses, Ferguson and his associates have shown that some of the inulin must be re-absorbed by the tubules, and that the re-absorption was related to P_r . The regression studies presented in the present paper seem to indicate that any re-absorption of inulin by the tubuli which may occur is of no importance to the reduction of the Cl_I figures in successive periods. This is so with regard both to human beings with normal kidney function and patients suffering from chronic disease of the kidneys. The comparatively slight reduction of the Cl_I figures in the latter group may presumably be traced to the anatomical changes in the kidneys with a resulting reduction of the functional regulation mechanism.

Summary and Conclusions.

After a single intravenous injection of inulin, the inulin clearance figures (Cl_I) fall from the first to the fifth period (Tables I & II). The difference between the Cl_I figures in the first and second period is not significant, but it is so from the third period. The fall in the clearance figures from the first to the third period is real. No evidence is found to show that, at some definite plasma concentration, there is a fall in the Cl_I figures. In cases of chronic renal disease (Tables III & IV) the difference between the means for the various periods is less marked than in the normal material.

The reduction of the Cl_I figures has been attributed to re-absorption of inulin by the tubules, but on the basis of our studies we believe we have proved that tubular re-absorption is not very likely as a causal factor. There are two factors which independently or in co-operation with each other can reduce the clearance figures. They are an increase of the intrarenal pressure and changes in the volume and composition of interstitial fluid. Presumably there exists in the kidneys a trigger mechanism in relation to the composition and distribution of extracellular fluid, and this mechanism is one of the main causes of the reduction of the Cl_I figures. When, in advance of the clearance periods, the patient is given fluids, they effect changes in the volume and tonicity of the extracellular fluid and in the intrarenal pressure. The time at which these changes take place corresponds to the time at which Cl_I is reduced. In order to eliminate these factors as much as possible, the volume of the interstitial fluid must be kept as constant as possible throughout the clearance periods.

References.

1. Black, D. A. K.: *Lancet* 264, 1953, 305. — 2. Brun, C., Hilden, T. & Raaschou, F.: *J. Clin. invest.* 28, 1949, 144. — 3. Ekehorn, G.: *Acta med. scand.* 118, 1944, 114. — 4. Ferguson, M. H., Olbrich, O., Robson, J. S. & Stewart, C. P.: *Quart. J. exper. physiol.* 35, 1950, 251. — 5. Guadino, M. & Levitt, M. F.: *Amer. J. Physiol.* 157, 1949, 387. — 6. Hogeman, O.: *Sv. Läkartidn.* 40, 1943, 2253. — 7. Josephson, B. & Lindahl, O.: *Acta med. scand.* 116, 1943, 20. — 8. Kruhoffer, P.: *Acta physiol. scand.* 11, 1946, 16. — 9. Landowne, M. & Alving, S.: *J. lab. & clin. med.* 32, 1947, 931. — 10. Laake, H.: *Acta med. scand., suppl.* 168, 1945. — 11. McCance, R. A. & Widdowson, E. M.: *J. physiol.* 91, 1937, 222. — 12. McSwiney, R. R. & Wardener, H. E.: *Lancet* 259, 1950, 845. — 13. Moyer, J. H., Conn, H., Markley, K. & Schmidt, C. F.: *Amer. J. physiol.* 167, 1950, 250. — 14. Robson, J. S., Ferguson, M. H., Olbrich, O. & Stewart, C. P.: *Quart. J. exper. physiol.* 35, 1950, 111. — 15. Schachter, D., Freinkel, N. & Schwartz, I. L.: *Amer. J. physiol.* 160, 1950, 532. — 16. Shipley, R. E. & Study, R. S.: *Amer. J. physiol.* 167, 1951, 676. — 17. Smith, H. W.: *Lectures on the kidney*. New York 1943. — 18. Smith, H. W.: *The Kidney*, New York 1951. — 19. Trueta, J., Barclay, A. E., Daniel, P. M., Franklin, K. J. & Prichard, M. M. L.: *Studies of the renal circulation*, London 1947.

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Heart Disease and Pregnancy. A Follow-up Study of a Hospital Material.

By

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We are not infrequently confronted by the question: Can or should women suffering from organic heart disease be allowed to become and continue pregnant. Here we are dealing not only with the immediate risk of pregnancy and confinement, but also with possible permanent ill effects of pregnancy on heart patients. The latter question concerned with the late prognosis, can to a certain extent be illuminated by a hospital material.

About 1880, women suffering from organic heart disease were warned against pregnancy, and a few doctors also advised such women not to marry. During the last 70—75 years there has been a complete revolution with regard to the calculation of the risk involved. This change must primarily be traced to a considerable reduction of the maternal mortality (from 55 % to 3.4 %) which is due not least to the fact that we now can select with greater certainty the heart patients who will probably be able to pass through pregnancy and confinement without too great a risk. In making this selection we continue still to be confronted by certain factors whose importance cannot be estimated with accuracy. In such cases it is absolutely necessary to individualize when the risks are to be calculated.

From the clinical point of view, the most important change in the circulation during pregnancy is the increase of the heart's minute volume. Earlier investigations have shown an average increase of 50 %, with a maximum reached in the ninth month followed by a fall before birth. With improved technique, Werkö and others (1948) have found that the minute volume increases by 1 litre between the fourth and ninth month of pregnancy. This increase depends partly on an increase of the stroke volume, and partly on a rise of the pulse rate. The plasma volume and the heart's minute volume run parallel, but there is no convincing proof that the increase of the former is directly responsible for the increase of the latter (Jones (1951)). During pregnancy the tissue fluid increase runs parallel with the plasma volume — in a way corresponding to events in a whole series of clinical and experimental conditions. A considerable sodium-ion retention occurs, on the average

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0.5 g per day (Chesley (1944)). This change is attributed to the increased production of steroid hormones. The water retention is to some extent secondary to the sodium retention, and to some extent to the increased oestrogen hormone level in the organism.

Several factors have been drawn into the discussion on the causes of the increase of the minute volume. Liljestrand (1945) and several others have drawn attention to the acidosis which is regularly to be found during pregnancy. The increase of weight during pregnancy is an important factor, but the change in the haemodynamic conditions of several organs also plays a part, in the case of the liver (Werkö, 1951), the kidneys (Bucht, 1951) and the skin (Burt, 1949) whose vascular circulation is increased. The circulation time diminishes right up to the last month of pregnancy. The pressure in the veins rises as does also that in the capillaries.

The organism's oxygen requirements increase uniformly during pregnancy and are up to 25 % above normal. This is partially compensated for by an increased arterio-venous oxygen difference in the mother. Gas analyses (Brown et al. (1947)) have shown that there is no arterio-venous shunt in the placenta, and tests with injections in situ (Earn & Nicholson (1952)) have confirmed this finding. We may therefore dismiss the assumption, put forward earlier, that an arterio-venous shunt in the placenta is responsible for the increase of the minute volume.

The blood pressure, the diastolic in particular, shows a falling tendency during pregnancy, but in the last month of pregnancy it again rises to normal and not infrequently still higher. There is also a fall of the blood pressure in the pulmonary circulation.

During pregnancy the capacity to respond to additional calls on the heart becomes 30—50 % of the normal. The normal heart possesses reserves to compensate for such calls. But we must bear in mind that during pregnancy women with healthy hearts not infrequently develop an effort syndrome with a labile, hyperactive heart action, sighing respirations, and precordial pain with apical localization. In the latter part of pregnancy more than half the women present a basal and apical systolic murmur and a triple cardiac rhythm.

American observers (Van der Veer & Kuo (1950)) have found organic heart disease in $1\frac{1}{2}$ % to 2 % of all pregnant women. Somewhat lower figures (0.7 %) have been found in Sweden (Westman (1945)). If these figures are applied to Norway where official statistics show that between 60,000 and 70,000 infants (64,103 in 1949) are born yearly, a not inconsiderable number of women suffering from organic heart disease must undergo pregnancy and confinement yearly. A comparatively great number of these women are unaware of their heart disease. If it is diagnosed before or at the beginning of pregnancy, the doctor in charge and the patient herself must take the difficult decision whether pregnancy is advisable or not — a decision in which ethical and social factors must count.

Own Material.

The material on which our analyses are based comes from the Medical Department B. of the Rikshospital and consists of the patients treated during the 10-year period

1942—1951. In the overwhelming majority of cases, the organic diseases of the heart in women of the child-bearing age are rheumatic or congenital. Our follow-up investigation was therefore concentrated on these types of heart disease. From the aetiological point of view, the hypertensive heart diseases constitute 1 %—2 % of the women in this age group. According to Goldring & Chasis (page 178) pregnancy is contra-indicated if the subjects of hypertonia show signs of impaired cardiac, cerebral or renal functions.

Some of our patients were re-examined in hospital in the spring and summer of 1952, and others have provided data concerning their health by answering questionnaires. Our material consists of 116 women who suffered from organic heart disease and who underwent pregnancy once or several times. Serving as controls were 56 nulliparae who suffered from organic heart disease and who were treated in our hospital in the above-mentioned decade. Table I shows the distribution of the various types of heart disease — a distribution almost identical with that of other observers. It is the patient suffering from mitral stenosis who presents the main problem when the relationship of organic heart disease to pregnancy is discussed. Anamnetic data concerning previous attacks of rheumatic fever were obtained in about half our cases (58 out of 109), and a third (37 out of 109) were aware of their rheumatic heart disease before they became pregnant.

Table I.

Number of cases of organic heart disease.

Rheumatic lesions	{	Mitral stenosis-insufficiency	90	} 94 %
		Aorta insufficiency-stenosis	7	
		Combined aortic and mitral disease	12	
		Sum	109	
Congenital lesions	{	Ductus Botalli	2	} 6 %
		Pulmonary artery stenosis	2	
		Auricular septum defect	2	
		The Eisenmenger syndrome	1	
		Sum	7	

We know from the literature that women suffering from organic heart disease can undergo numerous pregnancies. Postmortem records have shown that women suffering from third degree mitral stenosis have undergone 11 pregnancies without showing signs of heart disease and dying in old age of intercurrent disease (Graham et al. (1951)). Correll & Rosenbaum (1950) have presented their clinical material with confinements numbering from 4 to 18. Table II of our own material shows that approximately two-thirds of our patients had undergone one or two pregnancies, but there are also a few women who had given birth to many infants. In order to demonstrate the frequency with which these sufferers from organic heart disease were confined, we have presented in table III their offspring, expressed as a percentage, in comparison with the corresponding figures for Norway as a whole according to the census of December 3, 1946. As was to be expected, the number of heart patients giving birth to one or two infants was higher than that for the country as a whole. It is therefore surprising to find that the mean for the number

Table II.
Number of pregnancies per patient with organic heart disease.

Number of patients	Number of pregnancies.
37	1
38	2
18	3
7	4
6	5
4	6
3	7
2	10
1	11

of infants born to women suffering from heart disease is somewhat higher than for the country as a whole. Evidently this cannot be so in reality, and it is probable that we are misled by the composition of our material. The number of infants born to women suffering from congenital heart disease was somewhat lower than the corresponding number for cases of rheumatic heart disease (2.1 and 2.7 respectively). These women had undergone 301 pregnancies without complaining of subjective symptoms of heart disease, and seven of them had given birth to twins. In 11 cases (3.5 % of the pregnancies) abortion had had to be induced early in the pregnancy because of progressive heart complaints. This shows that *the number of women who suffer from organic heart disease and whose hearts give them trouble during their pregnancies is comparatively small*. In 22 cases subjective symptoms of heart failure made their appearance directly after confinement. Half of them were primiparae, and four of them gave birth to twins. According to Bunim and Rubricius (1948) the frequency with which heart patients present signs of decompensation after their first confinement reflects the strain of labour which is greatest in primiparae. The overwhelming majority of the patients whose pregnancy and confinement are associated with decompensation of the heart develop it during the puerperium.

There is a widespread conviction that many pregnancies are risky and should be avoided by the subjects of heart disease, but the investigations undertaken to solve this problem have yielded findings which are to some extent contradictory. In recent years observations (Bunim & Appel, 1950) have shown that there is no greater frequency of signs of heart failure among multiparae than among primiparae. To throw light on this problem, we have correlated the number of confinements among the subjects of rheumatic disease, and the number of years following the latest confinement before the patient develops signs of heart failure (fig. 1). This scatter-diagram shows a striking accumulation of cases of decompensation after the first and second confinements, but the diagram does not indicate any correlation. The correlation coefficient is 0.18 and is therefore not significant. It will thus be seen that *our material has not demonstrated any connexion between the frequency of heart failure and the number of births*.

Table III.

Percentage distribution according to the number of children.

Number of children	Percentage Tho whole of Norway	Own material
1	24.1	31.9
2	22.5	32.8
3	13.4	15.5
4	8.2	6.0
5	5.2	5.2
6	3.5	3.4
7	2.5	2.6
10	0.8	1.7
11	0.5	0.9
Mean	2.52	2.66

In addition to the influence of the number of births, the degree and localization of rheumatic valvular disease of the heart have been studied as being of prognostic significance. It has also been suggested that lesions arising after chorea minor have a better prognosis than lesions following rheumatic fever. Our observations show that patients with pure aortic lesions or combined aortic-mitral lesions do not show a higher rate of decompensation than patients suffering from pure mitral disease. Several writers have come to the same conclusion (Bunim & Rubricius (1948), Correll & Rosenbaum (1950), and Bunim & Appel (1950)). According to Bjerlöv, (1942), the functional condition of the myocardium is more important than the type and degree of the valvular disease of the heart.

Table IV.

Age at onset of heart failure in relation to the number of attacks of rheumatic fever.

	Mean age at onset of heart failure.	
	Nulliparae	Parae
One attack of rheumatic fever	33.6 (14.1)	39.1 (11.1)
Several attacks of rheumatic fever	40.7 (17.0)	40.4 (12.6)

According to Bunim and Appel (1950), the interval between the first attack of rheumatism and pregnancy is of prognostic significance, and it has been generally assumed that the subjects of rheumatic lesions should be confined at as early an age as possible. Fig. II shows the number of years between the first attack of rheumatic fever and the first pregnancy correlated with the number of years between confinement and the onset of signs of heart failure. As in earlier studies, our own study shows a weak negative correlation ($r = -0.15$) which shows that *the greater the interval between the first attack of rheumatic fever and confinement, the sooner do signs of heart failure follow confinement*. Neither for nulliparae nor for

CORRELATION OF THE NUMBER OF BIRTHS WITH THE
NUMBER OF YEARS PRECEDING HEART FAILURE

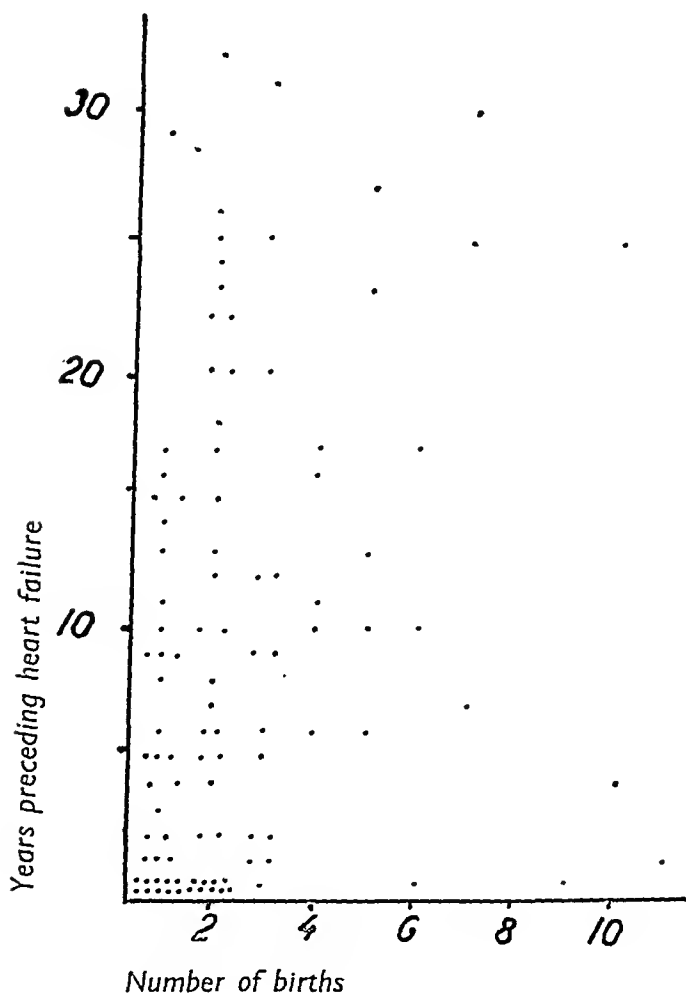


Fig. I.

multiparae does it matter to the prognosis whether there have been several attacks or only one of rheumatic fever. Table IV shows that there is no significant difference between the various groups with regard to the mean age at the onset of signs of heart failure. This is so because in the overwhelming majority of cases

CORRELATION OF THE NUMBER OF YEARS BETWEEN FIRST
ATTACK OF RHEUMATIC FEVER AND THE FIRST PREGNANCY
WITH THE NUMBER OF YEARS BETWEEN CONFINEMENT
AND HEART FAILURE

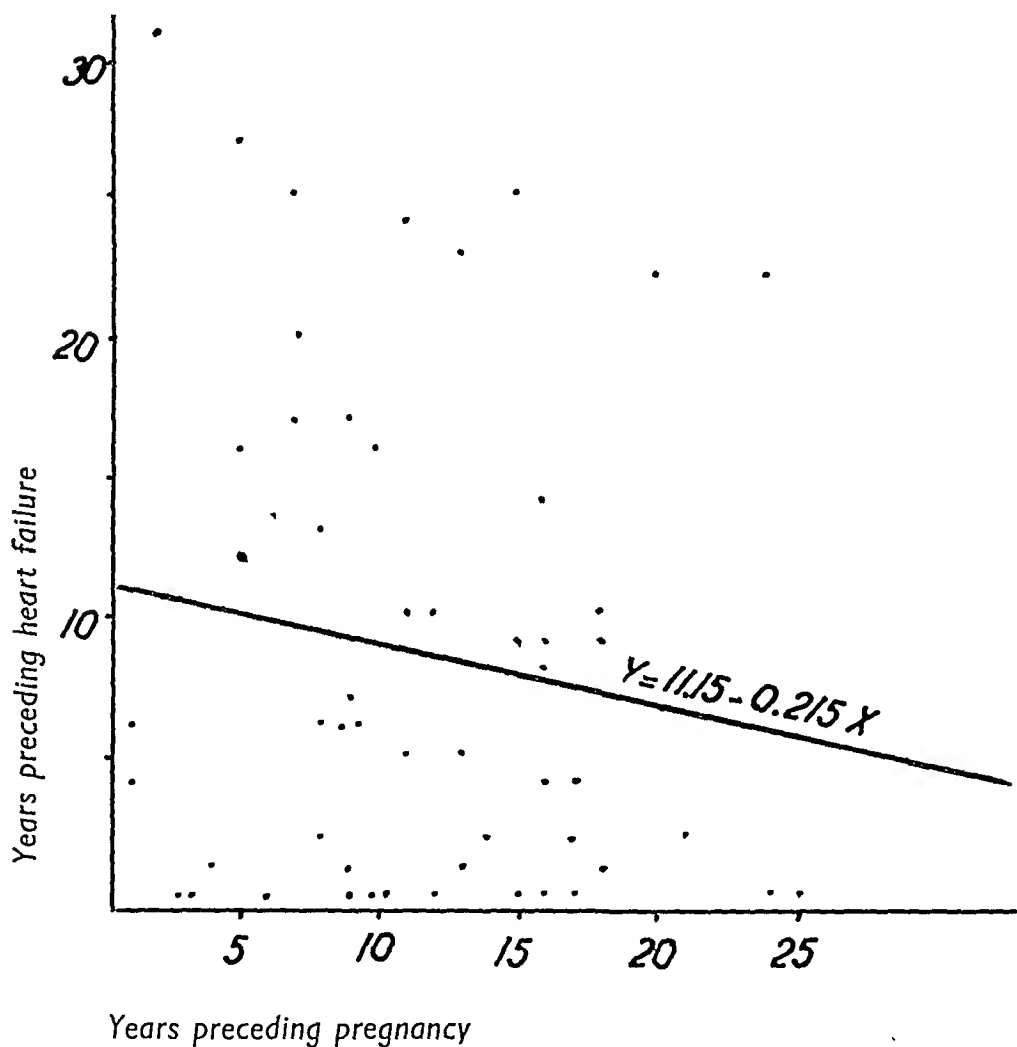


Fig. II.

it is the first attack of rheumatic fever which gives rise to valvular disease of the heart.

According to Bunim and Rubricius (1948), Correll and Rosenbaum (1950), and Van der Veer and Kuo (1950), the age of a heart patient at the time of her confinement is an important factor concerned with the development of heart

DISTRIBUTION OF WOMEN ACCORDING TO THEIR
AGE AT THE ONSET OF HEART FAILURE.
PATIENTS OVER 25 YEARS.
PERCENTAGE DISTRIBUTION IN EACH AGE GROUP.

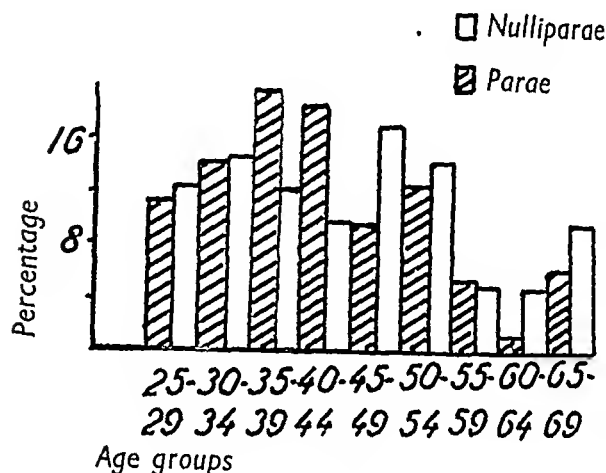


Fig. III.

failure, and according to Hamilton (1947) it is particularly after confinement after the age of 35 that the prognosis is bad. The age distribution of our patients does not permit of any exact, numerical estimate on this point, but if we place our patients in groups according as they were under or over the age of 30, and at the same time, according to the number of their confinements, we do not find that signs of heart failure set in earlier in the older than in the younger age group.

Table V.

Mean age at onset of heart failure and duration of observation period of heart failure.

	Mean age at onset of heart failure	Mean observation period of heart failure.	
		Living	Dead
Nulliparae	37.0 (15.1)	9.65 (9.3)	6.0 (3.8)
Parae	41.0 (11.7)	9.5 (5.9)	6.7 (4.25)
Difference and estimated sampling error.	4.0 (2.3)	0.15 (1.5)	0.7 (1.6)
Is the difference significant?	No	No	No

Various methods have been employed in determining the prognosis for heart patients who have been confined. The patient's age at the onset of signs of heart failure, and her age at death give the most adequate data for determining the prognosis. Fig. III shows that after the age of 25 and in the age groups 35-39 and 40-44, patients who have been confined are more often subject to decompensation of the heart than nulliparae, but the difference is not statistically significant. The mean age at the onset of signs of heart disease was 41 (11.7) for patients who had been confined, and it was 37 (15.1) for nulliparae (table V). The compar-

DISTRIBUTION OF WOMEN ACCORDING TO THEIR
AGE AT THE ONSET OF HEART FAILURE.
PERCENTAGE IN EACH AGE GROUP.
THE WHOLE MATERIAL.

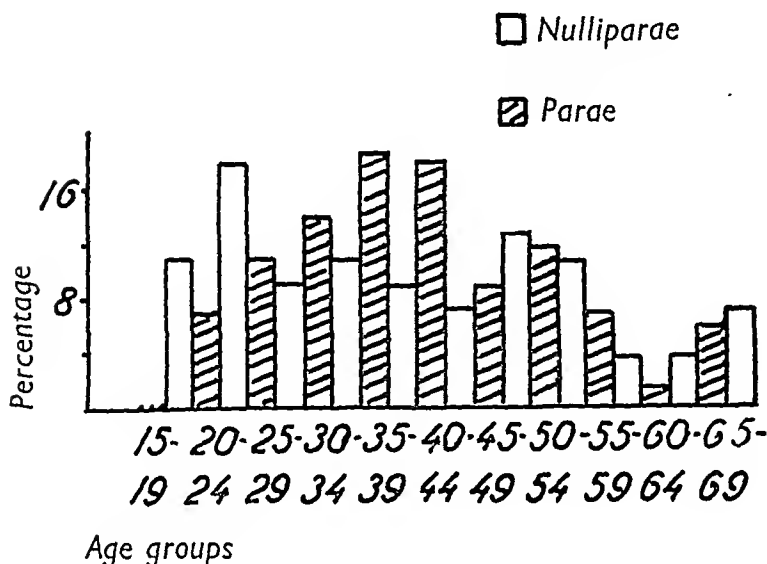


Fig. IV.

atively low mean age at the onset of asystole for nulliparae depends on a relatively great number of young patients with signs of heart failure in our material (fig. IV). Among our patients who had been confined there were 24 who were dead at the time of the follow-up investigation. The mean age at the time of death was 55.2 (11.85) for the patients who had been confined and 34.3 (10.15) for the nulliparae. For the sake of comparison we would quote Aubert (1943), whose study of rheumatic patients in Bergen showed a mean age at the time of death of 43 $\frac{1}{3}$ years. Boyer and Nadas (1944) found the mean age to be 51.5 years for women who had been confined. Other writers also have found the mean age at the time of death to be younger for nulliparae than for multiparae. In order to obtain a comprehensive survey of our prognosis studies, we have presented in table V the mean age at the time of onset of signs of heart failure and the observation period with heart failure for the two groups of patients. We have found in this material no statistically demonstrable difference between the women who had been confined and nulliparae.

Our cases of congenital heart disease show that most types of acyanotic lesions are not unfavourably influenced by pregnancy. These patients had undergone from one to four pregnancies without experiencing any aggravation of their disease. But a greater number of pregnancies is not advisable. Ductus arteriosus persistens

Botalli, isolated stenoses of the pulmonary artery, and septum defects of the auricles and ventricles do not contra-indicate pregnancy provided there is no considerable enlargement of the heart (Taussig (1947), Van der Veer and Kuo (1950)). Women suffering from coarctatio aortae ought not to undergo pregnancy, and the same prohibition applies to the subjects of congenital lesions when they suffer from persistent cyanosis (Taussig). The maternal mortality for patients suffering from congenital heart disease is 2.9 % according to Hamilton (1947).

Discussion.

The statistical calculations on which our conclusions are based show that our material is numerically sufficiently representative. In a clinical material such as ours there must inevitably be certain defects, and they apply particularly to the control group of nulliparae. This is why some writers have employed males suffering from rheumatic lesions as controls (Cohn and Lingg (1943), Graham et al. (1951)). It was also found that the duration of life was practically identical for men and parous women. Some women with rheumatic lesions die before reaching the nubile age, and others suffer so much from their heart disease early in the fertile age that they do not marry. This is why the group of women who suffer from rheumatic lesions, who marry and who give birth to children represent a selective group consisting of women suffering from lesions which give rise to insignificant symptoms or none at all. The social conditions under which a patient lives are also of prognostic significance, and we must remember that our calculations are based on the patient's own statements with regard to the onset of asystole, and this may constitute a source of error. These sources of error have been eliminated in the larger American materials, and it has thus been possible to study comparable groups. Cohn and Lingg (1943) have done this, and like us they have found no significant difference in the clinical course run by the subjects of rheumatic heart disease and in the expectation of life according as the patients were parous or nulliparae.

Even though these investigations show that the prognosis is good for women who suffer from heart disease and are confined, we must not ignore the fact that pregnancy and confinement represent an increased risk for the subjects of rheumatic lesions. In an American material (Bunim and Appel) the maternal mortality in the 10-year period 1936—48 was 3.4 %, and the risk was approximately four times greater for the patients suffering from decompensation during pregnancy than for the compensated cases (Van der Veer and Kuo). In the overwhelming majority of cases the cause of death was heart failure, but embolism and bacterial endocarditis occurred also (Hamilton). In one of our cases a subacute bacterial endocarditis developed post partum. Reactivation of a rheumatic carditis is very seldom seen during pregnancy. There is also a rise of the infant mortality when the mother suffers from heart disease, and this rise is greatest when the mother's heart disease is decompensated (Bunim, Appel and others). The relatively high infant mortality usually depends on prematurity (Van der Veer and Kuo).

Our material shows that in several cases of rheumatic disease decompensation

set in directly after the first or second confinement. We are under the impression after a closer analysis of these cases that in most of them a correct selection would have led to the advice not to become pregnant. The heart's functional capacity to respond to work is undoubtedly the most reliable guide to such a selection, even though we do not possess exact methods for determining heart reserves. Such selection is guided by the rules laid down by the American Heart Association for cardiac insufficiency. Patients belonging to Group I with very small radiologically demonstrable enlargement of the heart run but small risks on becoming pregnant (mortality < 1 %). Patients belonging to Group II, with moderate enlargement of the heart show a mortality of about 5 % in connexion with pregnancy, while patients in Group III show a mortality far above 10 %. Patients who by functional tests belong to Group III or Group IV should be advised against pregnancy, as should also the subjects of active rheumatic carditis or permanent fibrillation arrhythmia. A record of signs of a failing heart during earlier pregnancies should also be a contra-indication.

Even when these rules for the selection of candidates for pregnancy are followed, patients belonging to Groups I and II may suffer from decompensation during pregnancy. When signs of heart failure set in before the fourth month of pregnancy, the induction of abortion is recommended, possibly supplemented by sterilization (Van der Veer and Kuo). Later on in pregnancy the risk entailed by an operation is greater than that incurred by allowing the pregnancy to continue to term. Sterilization was carried out in 15 of our cases, in conjunction with the induction of abortion in 8, and after confinement in the other cases. There is convincing statistical evidence to show that abstention from operative treatment of heart patients in the latter part of their pregnancy and during confinement yields the smallest maternal mortality. The treatment of cardiac insufficiency is based on the ordinary principles of medicine. A recent report from England (Logan and Turner) is to the effect that mitral valvulotomy is indicated when women suffering from mitral stenosis begin to show signs of heart failure early in pregnancy. The operation risk does not seem to be increased by pregnancy, and thoracotomy before the fourth month of pregnancy does not increase the risk of abortion.

The line of conduct to be chosen is comparatively clear when we are dealing with rheumatic or congenital lesions in connexion with pregnancy. But we are not on such safe ground when we have to make our choice for patients who have suffered from infarct of the heart, subacute bacterial endocarditis or have undergone some operation for congenital lesions. We know from the literature of the subject that women have survived pregnancy after contracting bacterial endocarditis (Hamilton), infarct of the heart (Horwitz et al.) and after undergoing intracardiac operations (Russell et al.). But we have not yet any great experience with regard to these conditions when considering the advisability of pregnancy.

Conclusions and Summary.

The change in the haemodynamic conditions during pregnancy constitutes an additional strain on the heart, and an effort syndrome develops not infrequently

during the pregnancies of women with healthy hearts. As some 2 % of pregnant women suffer from organic heart disease, we are fairly often confronted by the problems raised by the combination of the two conditions.

In order to study the late prognosis for women who have been confined after suffering from rheumatic and congenital heart disease, we have undertaken a follow-up investigation of a medical hospital material. Table I shows the distribution of the various types of heart disease and the numerical superiority of cases of mitral stenosis. Table II shows that most of the subjects of organic heart disease had undergone one or two pregnancies, but when we compare the number of children born to heart patients with the number of children born in the whole of Norway, we find that the mean for the two groups is almost identical (table III). In the present material our patients had undergone 312 pregnancies, and in only 3.5 % of them had signs of heart failure developed and led to the interruption of pregnancy. By correlating the number of births with the number of years between the last confinement and the appearance of heart failure (fig. 1) no connexion could be established between the number of confinements and the frequency of heart failure. To judge by our investigations, the localization of rheumatic valvular disease of the heart is of no prognostic significance. Fig. II deals with a correlation calculation which shows that the longer the interval between a first attack of rheumatic fever and confinement, the shorter is the period between confinement and the subsequent development of heart failure. Table IV shows that the prognosis is influenced neither for nulliparae nor parae whether they have had one attack of rheumatic fever or several. In the present material the late prognosis was not influenced by the patient's age at the time of her confinement. Table V shows the mean age at the onset of heart failure, nulliparae being somewhat younger than parae. This was so presumably because there was a comparatively great number of young patients suffering from heart failure in our material (fig. IV). The mean age at the time of death was 55.2 years for parae and 34.3 years for nulliparae.

Our material shows that pregnancy is not contra-indicated for women with congenital lesions — ductus arteriosus persistens Botalli, isolated stenosis of the pulmonary artery and septum defects of the auricles and ventricles.

The follow-up examination presented here shows that the late prognosis is good for women who suffer from rheumatic lesions and who survive pregnancy, and that it is probable that the maternal mortality can be still further reduced by a correct selection of prospective mothers.

References.

- Aubert, A. Boeck, *Bidrag til hjertesykdommenes etiologi og prognose*. Bergen 1943. — Bjerlov, H. *Nord. Med.* 14, 1701, 1942. — Boyer, N. H. and Nadas, A. S., *Ann. Int. Med.* 20, 99, 1944. — Brown, E., Sampson, J. J., Wheeler, E. O., Gundelfinger, B. F. and Gian-siracusa, J. E., *Amer. Heart Journ.* 34, 311, 1947. — Bucht, H., *Studies on renal function in man*, Stockholm 1951. — Bunim, J. J. and Appel, S. B., *J. A. M. A.* 142, 90, 1950. — Bunim, J. J. and Rubrieus, J., *Amer. Heart Journ.* 35, 282, 1948. — Burt, C., *Lancet* 257, 787, 1949. — Chesley, L. C., *Amer. Journ. Obstet. & Gynecol.* 48, 565, 1944. — Cohn, A. E. and Lingg, C., *J. A. M. A.* 121, 1 and 113, 1943. — Cohn, A. E. and Lingg, C., *cit.*

Correll and Rosenbaum. — Correll, H. L. and Rosenbaum, F. F., *Amer. Heart Journ.* 39, 283, 1950. — Earn, A. A. and Nicholson, D., *Amer. Journ. Obstet. a. Gynecol.* 63, 1, 1952. — Graham, G. K., Taylor, J. H., Ellis, L. B., Greenberg, D. J. and Robbins, S. L., *Arch. Int. Med.* 88, 532, 1951. — Hamilton, B. E., *Amer. Heart Journ.* 33, 663, 1947. — Horwitz, O, La Plaze, L. B., Shumway, N. P. and Stroud, W. D., *J. A. M. A.* 121, 1342, 1943. — Jones, A. Morgan, *Heart disease in pregnancy*, London 1951. — Liljestrand, G., *Nord. Med.* 27, 1852, 1945. — Logan, A. and Turner, R., *Lancet* 262, 1286, 1952. — Russell, K. P., Dallke, W. E. and Buell, J. I., *J. A. M. A.* 149, 266, 1952. — Taussig, H., *Congenital malformations of the heart*, New York 1947. — Van der Veer, J. B. and Kuo, P. T., *Amer. Heart Journ.* 39, 2, 1950. — Werkø, L., *Nord. Med.* 45, 450, 1951. — Werkø, L., Bucht, H., Lagerlöf, H. and Holmgren, A., *Nord. Med.* 40, 1868, 1948. — Westman, A., *Nord. Med.* 27, 1864, 1945.

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Suprasternal Puncture of the Pulmonary Artery.

By

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(Submitted for publication September 17, 1953.)

The suprasternal technique of left atrial puncture is employed by us for flow studies in certain affections of the cardiovascular system (S. Radner, in press). While aiming at the left atrium by this approach, the needle was passed into the pulmonary artery in three cases. The procedure was entirely harmless to the patients. The unintended punctures were utilized for measurements of the pressure variations in the lesser circulation.

There are close anatomical relationships between the left atrium and the pulmonary artery which explain the aberration of the needle.

Anatomical Notes.

The main stem of the pulmonary artery bifurcates over the anterior portion of the left atrium, and its right branch turns around the posterior aspect of the ascending aorta, in front of the tracheal bifurcation (Fig. 1). When the needle is guided closely along the anterior border of the trachea, it penetrates as a rule directly into the left atrium, behind the right pulmonary artery. If the direction of the needle is slightly more anterior, the right pulmonary artery may be punctured. By the suprasternal approach, the pulmonary artery is entered through its extrapericardial wall, while the left atrium in most cases is reached through the pericardial cavity. If by this approach the insertion of the needle is continued right through the pulmonary artery for one or two more cm, the left atrium will be reached after penetrating the transverse pericardial sinus, which separates the two structures.

Technical Notes.

A special double needle is employed which permits safe puncture and easy handling for aspiration, flushing and pressure measurement. The external diameter of the outer needle is 0.8 mm, and its free length is 165 mm.

After local anaesthesia (without adrenalin) of the skin and subcutaneous layer towards the upper thoracic aperture, the needle is inserted in the midline 3—4 cm above the bottom of the suprasternal fossa; if it is inserted directly into the fossa, the skin will form a pursing funnel around it. The needle is directed posteriorly to the aortic arch, which is felt pulsating at a depth of about 1—6 cm below the level of the fossa. Advancing closely along the trachea in the midline, a softly

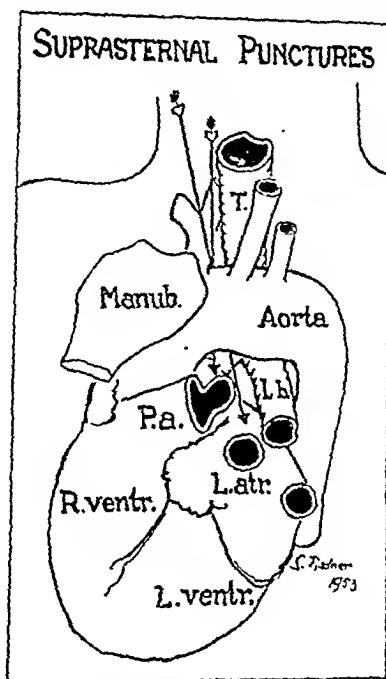


Fig. 1. Drawing to show the anatomical relationships of the pulmonary artery. Arrows indicate the direction of suprasternal puncture of the pulmonary artery and the left atrium.

T. = Trachea. L. b. = Left main bronchus.

P. a. = Pulmonary artery, cut to show first part of its right branch.

pulsating resistance is felt with the needle at a depth of about 8—16 cm below the fossa. It is impossible to decide, judging solely from the character of this resistance, whether the needle rests on the pulmonary artery or on the left atrium. Only after puncturing and aspiration of blood or pressure measurement can the position be determined. If the needle has been found to stand in the pulmonary artery, we do not hesitate to introduce it further for left atrial puncture.

For pressure recordings, the needle is connected with a Tybjaerg Hansen manometer by means of a short piece of a Cournand catheter.

Notes on the Results.

The pulmonary artery was unintentionally punctured by the suprasternal approach in three cases out of six, the left atrium being the point of destination of the

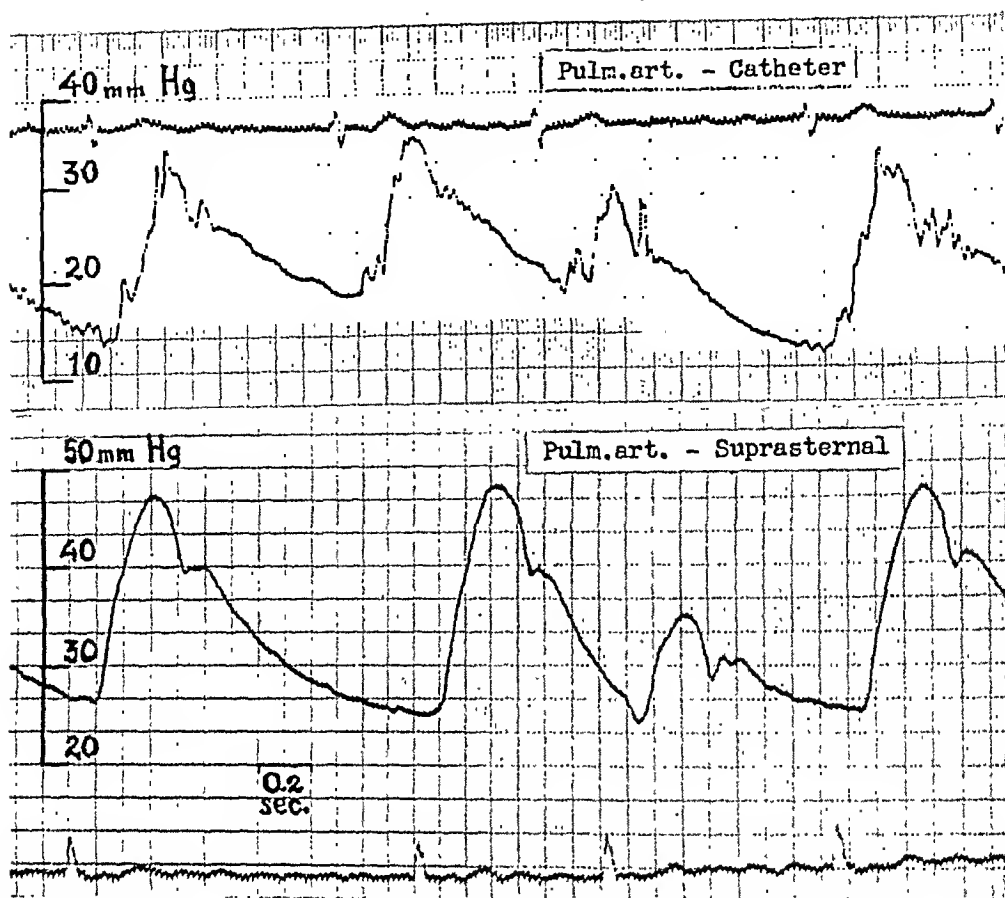


Fig. 2. Pressure curves taken from same point in the right pulmonary artery, the upper curve by right heart catheterization, the lower by suprasternal puncture. The catheter curve shows mechanical interference due to oscillations of catheter. There is no extraneous distortion of the suprasternal curve. Both curves obtained from a patient with mitral stenosis and secondary pulmonary hypertension. Interval of two days between the two procedures.

needle. In all of the cases, right heart catheterization had been performed prior to the puncture, and therefore the pressure levels in the pulmonary artery were already known. However, the percutaneous pressure curves seem to afford important additional information of the pulmonary hemodynamics.

Pressure tracings from the pulmonary artery obtained by right heart catheterization regularly show mechanical interference due to oscillations of the catheter, and this renders impossible the detailed analysis of the curve patterns. The pressure records obtained by suprasternal puncture of same vessel do not show such extraneous distortion, and hence wave contour analysis may be applied for right heart outflow studies. The difference in shape between the two types of records is demonstrated in fig. 2.

Owing to the relatively small size of the target, attempts at selective puncture of the pulmonary artery are not being planned. The present frequency of accidental

punctures of the artery suggests, however, that continued use of our left atrial procedure will provide sufficient material for a systematic study of right heart outflow by wave contour analysis.

Summary.

While attempting left atrial puncture by the suprasternal technique, the pulmonary artery was punctured in three cases out of six. The pressure curves from the artery obtained by this technique did not show the distortion by extraneous interference regularly seen in corresponding curves taken through heart catheterization. The suprasternal pressure tracings therefore permit flow studies by wave contour analysis.

References.

S. Radner: Suprasternal puncture of the left atrium for flow studies. *Acta med. scand.*, 1954, 148. 57.

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Electrophoretic Studies of Red Cell Hemolysates.

By

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(Submitted for publication May 22, 1953.)

It has been known for already some time that the hemoglobin of human red cells during fetal life differs from the hemoglobin of a healthy adult in certain chemical, physical and physiological respects. Already in the nineteenth century it was found that the hemoglobin of the fetus is more slowly denatured than that of the adult in an alkaline solution (14, 15). Later Brinkman and Jonxis made further developments in this method and studied the behavior of the hemoglobin of the fetus, infant and adult toward alkaline denaturation (6, 7).

Barcroft assumed that the hemoglobin of persons with anemia resembles fetal hemoglobin in certain respects (5). Using the method of Brinkman and Jonxis, Larsen studied the red cells and their hemolysates in pernicious anemia (17). He demonstrated that in these red cells alkaline hematin is formed from the hemoglobin in the same manner as in a mixture containing fetal and healthy adult blood in equal proportions. It was also seen that the hemoglobin from the normocytes of these patients conformed to the hemoglobin of the healthy adult, whereas the hemoglobin from macrocytes (that portion of the red cells not hemolysed in a 0.30 per cent saline solution) was still more resistant to alkali than fetal hemoglobin.

A large number of electrophoretic experiments have been carried out with pure solutions of hemoglobin (*e. g.*, 8, 16) but Stern and his co-workers (23) were the first to publish, in 1945, a report on the electrophoretic pattern of red blood cell proteins. Previously there had been a report (2) comparing the electrophoretic mobilities of adult and fetal hemoglobin. It was demonstrated that fetal hemoglobin had a more rapid rate and separated from a mixture containing equal proportions of hemoglobin solution from adult and fetal red cells. Hoch (9) is also reported to have observed similar, though less marked, differences.

Pauling and his co-workers (18), in a study which aroused great interest on its publication in 1949, demonstrated that the hemoglobin of patients with sickle cell anemia differs electrophoretically from normal hemoglobin and forms a component of its own (S Hb). The hemoglobin samples of some persons with the sick-

ling trait were electrophoretically normal (N Hb), whereas other samples had a velocity corresponding to that of patients with sickle cell anemia. These studies were later supplemented by other reports (19, 26), and individual cases have also been described in which additional electrophoretic deviations from the normal were seen in the hemoglobin in anemias associated with hereditary coincidences (10, 11, 12, 13, 24).

Singer and his co-workers (20) developed an accurate method for examination of the denaturation of hemoglobin by alkali. They compared the abnormal behavior of the hemoglobin in electrophoresis and the values in alkali denaturation in sickle cell anemia but found no correlation. The group of miscellaneous diseases in their fairly extensive series included two untreated cases of pernicious anemia, in which elevated denaturation values were obtained. This appears to bear out the findings made by Larsen (17).

The electrophoretic studies thus far made on pathological or abnormal hemoglobins have been chiefly concerned with the hemoglobin in sickle cell anemia and in fetal red cells. No studies on diseases of the blood other than those mentioned above have been reported in the literature available to the author. Since disturbances in the protein synthesis of the red cells may also be present in other anemic conditions, an interesting problem is presented by the question as to whether electrophoresis reveals any features deviating from the normal in the hemoglobin or the red cell hemolysate in some of the more common anemias. The following is a description of the author's work in which an attempt was made to shed light on this question.

Material and Methods.

The series consists of blood samples taken from 13 healthy adults, 11 patients with pernicious anemia and 17 patients with other types of anemia. It also contains the blood sample from a case of polycythemia vera. Samples of umbilical cord blood from 9 new-born infants were also studied. The series thus totalled 51 samples.

The blood samples were heparinized or citrated, and centrifuged. The cells were washed three or four times in sterile physiological saline and some of the samples were then saturated with carbon monoxide for the purpose of comparison. Hemolysis was carried out with sterile distilled water and some of the samples were also treated with toluene. The cell stromata were centrifuged off and the bright red hemoglobin solution was stored before use in the refrigerator at $+4^{\circ}$ — $+6^{\circ}$ C (some of the samples in CO saturation). The length of storage time was usually 1–4 days, but in some cases it was only about 2 hours. Dialysis and electrophoresis were carried out with the instruments of the Antweiler apparatus (3, 4), using the following buffer solutions: Dole buffer, pH 8.6 (35 analyses), Michaelis buffer, pH 9.1 (2 analyses), and phosphate buffers, pH 6.9 and 7.2 (14 analyses). The time of dialysis varied from $1\frac{1}{2}$ to $2\frac{1}{2}$ hours. After dialysis the hemolysed solution was diluted to the suitable concentration of 0.5–1.5 per cent.

The samples were analysed either singly or in pools of 2–5 samples in Antweiler's micro-electrophoretic apparatus, using a running time varying from 8 to 80 min. (In serum analyses a run of 18 min. is usually sufficient.) A current of 1.10–2.25 mA and a voltage of 50–95 V was used. Reliable measurement of the potential gradient and the velocity was not possible in this system, one of the reasons being such great momentary

variations in the amperage and voltage that they could not be entirely compensated. The course of the analysis was followed by the Philpot-Svensson system (4, 25) and the results were registered by photography and/or interferometry (3, 4).

As controls, parallel analyses were made in 9 cases in the State Serum Institute, using the Tiselius apparatus.

The anticoagulants, carbon monoxide saturation and the buffer solutions used appear to have no influence on the final results of analysis. Table 1 shows the results of 9 analyses made on the blood of 7 healthy adults in the control group (N = normal) and the results of 17 analyses of the umbilical cord blood of 9 newborn infants (F = fetal). In some of the cases there was a single clear peak (type I), of which Fig. 1 is an example. Sometimes there was a small, more or less clear additional peak at the foot of the descending boundary (type II), which disappeared fairly soon (Fig. 2). In type III the peak was clearly broken into two or more boundaries (Fig. 3).

Table 2 lists along the same principles the patients with anemia, showing the analysis results, their dependence on the electrophoretic test conditions, and the hematological condition of the patient at the time the sample was taken. The diagnosis was based on the blood picture, the typical bone marrow finding, and other observations at clinical examination. Three patients in the pernicious anemia group (No. 9, 12 and 14) had already received specific treatment (2, 2 and 4 weeks), whereas the other patients had had no treatment.

Some of the samples were pooled, so that 2 to 5 samples were analysed together

Table 1.

Control series.

Electrophoretic conditions and results. — Apparatus: T = Tiselius, A = Antweiler. — Buffer: D = Dole, P = phosphate, M = Michaelis. For the Tiselius apparatus the potential gradient (Volts per cm) is given instead of the amperage and voltage. — Results: Type I = curve as in fig. 1; type II = curve as in fig. 2; type III = curve as in fig. 3 (see text).

Patient Group No.	Apparatus	Buffer	Electrophoretic conditions				Result	Patient Group No.	Apparatus	Buffer	Electrophoretic conditions				Result
			pH	V.	min.	mA.					pH	V.	min.	mA.	
Healthy adults								Newborn							
1.....	A	D	8.6	60	8	1.58	I	F 4 + N.....	A	P	7.2	75	38	1.75	I
2.....	A	D	8.6	72	18	1.50	I	F 2 + N.....	A	P	7.2	55	80	1.85	III
3.....	A	D	8.6	75	13	1.80	I	F 3 + F 4 + N	A	P	7.2	55	72	1.80	I
4.....	A	D	8.6	65	31	1.70	I	F 5 + N.....	A	P	7.2	85	60	2.00	III
5.....	A	D	8.6	90	45	2.00	III	F 5 + N.....	A	P	7.2	55	46	1.82	I
6.....	A	D	8.6	80	14	1.80	I	F 5 + N.....	A	M	9.1	55	45	1.80	I
6.....	A	D	8.6	95	45	2.05	III	F 5 + N.....	A	D	8.6	75	43	1.40	I
7.....	A	D	8.6	80	16	1.70	I	F 4 + N.....	A	D	8.6	60	60	1.10	I
7.....	A	D	8.6	80	30	2.25	III	F 6.....	T	P	7.2	5.7	600		II
								F 7.....	T	P	7.2	5.7	600		I
								F 8.....	T	P	7.2	8.9	540		III
								F 9.....	T	P	7.2	8.9	540		III
								F 9.....	A	D	8.6	95	26	2.00	III
New-born															
F 1.....	A	D	8.6	65	18	1.50	II								
F 2.....	A	D	8.6	65	22	1.40	I								
F 3+4...	A	D	8.6	75	17	1.65	II								
F 4.....	A	P	7.2	75	22	1.70	II								

Table 2.
Anemia series.

Hematological condition, electrophoretic conditions, and results.

Explanations as in Table 1 and as follows: Rbc. = Red blood cells in millions per c.mm.; L. = Color index; Hb = Hemoglobin percentage as determined with Hemotest, electrocolorimeter.

[illegible]

(Table 2). It was originally intended to find out by elimination the origin of the protein fraction which sometimes separated from the main peak, as measurement of the velocity was not considered possible in view of the uncertainty of the results under these conditions. In this way it would have been possible to compare the mobilities of the normal and the diverging component.

Results.

It is seen from the tables that the splitting up of the peak was only obtained in those analyses in which a higher amperage than usual (generally over 1.90 mA) was applied for a fairly long time. Thus the result is clearly dependent on the electrophoretic test conditions. «Normal» test conditions gave consistently a single peak or at the most a slight blurring. The anemia group showed no distinct difference from the normal group. In the new-born group there was quite frequently a doubtful result (type II), but a distinct splitting up of the peak occurred only when the current was stronger than normal. There can hardly be here a question of the separation of hemoglobins of type F and N (Andersch et al., 2). A result diverging from the others (type III) was obtained for pooled bloods No. I (Table 2). The same components with the exception of secondary anemia (acute leukemia) were included in pooled bloods No. II, which gave a negative analysis (single peak). The patient died before a control sample could be obtained.

The results of the 9 analyses carried out with the Tiselius apparatus point in the same direction as the results obtained with the Antweiler apparatus.

Discussion.

When the analysis is being followed by the Philpot-Svensson system in the Antweiler micro-electrophoretic apparatus there appears to be a certain degree of indefiniteness in the protein curve while phoresis is going on, no matter whether it is a question of serum or plasma proteins or, as in this work, of red cell proteins, *i. e.*, almost solely hemoglobin. Not even the slightest fraction preceded the hemoglobin peak, but in one or two other analyses carried out by the author, in which the centrifuged solutions were not quite clear, I observed a small peak which had a greater velocity than hemoglobin and which seemed to conform to the «a» protein observed by Stern and his co-workers (23). The ascending boundary of the hemoglobin peak was always intact, clearly defined and abrupt. On the other hand, at the lower part of the descending boundary of the peak there was sometimes a small additional peak, which disappeared when the current was cut off. There were also all intermediary patterns up to complete splitting up of the peak. The latter phenomenon may be ascribed merely to a convection phenomenon — in other words, decomposition — which is not identical with the «natural» fractionation of proteins in electrophoresis (1, 4, 25, 27). This seems to be indicated by the facts that the splitting of the peak usually started only after a relatively long electrophoretic run and always when a higher amperage than normal was used and that it was a highly variable, non-uniform and frequently merely a passing phenomenon.

No distinct difference was seen between the analysis results in the anemia group and in the normal series in any of these cases. This cannot be considered unexpected (20, 21, 22) and it does not conflict with the results obtained by Larsen (17). On the contrary, Singer and his co-workers have stressed a number of times in their reports that the electrophoretic curve merely depicts the migration of the proteins in the electric field. The different proteins which move together in this curve may well show differences in other respects, as also was proved by these workers (21, 22).

Summary.

1. Using Antweiler's micro-electrophoresis method the red cell proteins were examined in 51 blood samples taken from healthy adults, new-born infants (umbilical cord blood) and patients with different types of anemia.

2. No distinct variations from the normal were seen in pernicious anemia or in other types of anemia.

3. With the method used, the hemoglobin obtained from the red cells of the new-born was not clearly seen to differ in electrophoresis from the hemoglobin of the healthy adults.

4. Under the influence of over 1.90 mA applied for a sufficiently long period (and only exceptionally under «normal» conditions) the single peak given by the hemoglobin split up in all cases. However, this probably was only a convection phenomenon.

References.

1. Abramson, H. A., Moyer, L. S., and Gorin, M. H.: *Electrophoresis of Proteins and the Chemistry of Cell Surfaces*. Reinhold, New York 1942.
2. Andersch, M. A., Wilson, D. A., and van Menten, M. L.: *J. Biol. Chem.* 1944: 153: 301.
3. Antweiler, H. J.: *Kolloid-Ztschr.* 1949: 115: 130.
4. Antweiler, H. J.: *Die Quantitative Elektrophorese in der Medizin*. Springer, Berlin-Göttingen-Heidelberg 1952.
5. Bareroff, J.: Quoted by Larsen.
6. Brinkman, R., and Jonxis, J. H. P.: *J. Physiol.* 1935: 85: 117.
7. Brinkman, R., and Jonxis, J. H. P.: *J. Physiol.* 1937: 88: 162.
8. Davis, B. D., and Cohn, E. J.: *J. Am. Chem. Soc.* 1939: 61: 2092.
9. Hoch, H.: in Leeks H., and Wolman, I. J.: *Am. J. M. Sc.* 1950: 219: 684.
10. Itano, H. A., and Neel, J. W.: *Proc. Nat. Acad. Sc.* 1950: 36: 613.
11. Itano, A. H.: *Proc. Nat. Acad. Sc.* 1951: 37: 775.
12. Itano, A. H.: *Fed. Proc.* 1952: 11: 235.
13. Kaplan, E., Zuelzer, W. W., and Neel, J. W.: *Blood* 1951: 6: 1240.
14. von Körber, E.: Quoted by Brinkman and Jonxis.
15. von Krüger, F.: Quoted by Brinkman and Jonxis.
16. Landsteiner, K., Longsworth, L. G., and van der Scheer, J.: *Science* 1938: 88: 83.
17. Larsen, G.: *Proc. Intern. Soc. Hematology* 1950, p. 25.
18. Pauling, L., Itano, A. H., Singer, S. J., and Wells, I. C.: *Science* 1949: 110: 543.
19. Pauling, L., Itano, A. H., Wells, I. C., Schroeder, W. A., Kay, L. M., Singer, S. J., and Corey, R. B.: *Science* 1950: 111: 459.
20. Singer, K., Chernoff, A. J., and Singer, L.: *Blood* 1951: 6: 413.
21. Singer, K., and Chernoff, A. J.: *Blood* 1952: 7: 47.
22. Singer, K., and Fisher, B.: *Blood* 1952: 7: 1216.
23. Stern, K. G., Reiner, M., and Silber, R. H.: *J. Biol. Chem.* 1945: 161: 731.
24. Sturgeon, Ph., Itano, H. A., and Valentine, W. N.: *Blood* 1952: 7: 350.
25. Svensson, H.: *Ark. f. kemi, min. oeh geol.* 1946: 22 A: 10.
26. Wells, I. C., and Itano, H. A.: *J. Biol. Chem.* 1951: 185: 65.
27. Wiedemann, E.: in Wuhrman and Wunderly: *Die Bluteiweisskörper des Menschen*. Schwabe, Basel, 1947.



Fig. 1. Type I. Mixture of normal (N) and fetal (F) blood. Dole-buffer pH 8.6, 70 V, 1.65 mA, 28 min.



Fig. 2. Type II. Patient No. 21 (hemolytic anemia). Dole buffer pH 8.6, 90 V, 2.05 mA, 33 min.



Fig. 3. Type III. Patient No. 13 (pernicious anemia). Dole buffer pH 8.6, 90 V, 2.10 mA, 33 min.

WARIS: Electrophoretic Studies of Red Cell Hemolysates.

From the Ziskind Laboratories (Blood Research Laboratory) of the New England Center Hospital, and the Department of Medicine, Tufts College Medical School, Boston, Mass., U. S. A.

Direct Observations of Intravascular Agglutination of Red Blood Cells in the Cheek Pouch of Hamsters with Experimental Hetero-Immune Hemolytic Anemia.

By

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(Aided by Grants from the Rockefeller Foundation
and the

American Cancer Society (Massachusetts Division).

(Submitted for publication August 8, 1953.)

In 1938 and 1940, Dameshek and Schwartz (1, 2) pointed out that hemolytic anemia may be caused by antibodies which destroy the red cells in vivo. In those days, the methods used for detecting these antibodies were usually unsatisfactory. Since then, several new techniques have been developed, and erythrocytic antibodies are now demonstrable in most cases of erythroblastosis fetalis and acquired hemolytic anemia. The Coombs' test, which reveals a globulin adsorbed to the red cell surface, is usually positive in these two groups of immuno-hemolytic anemia (3, 4). Free agglutinin is found in the serum in many cases of acquired hemolytic anemia, and in some there is free hemolysin (amboceptor) (4, 5). The various methods for demonstrating antibodies, both those adherent to the red cells, and free in the serum, as complete or incomplete agglutinins, or free hemolysins have all proved very helpful. It should always be borne in mind, however, that these techniques show simply that there are proteins in the blood which act as auto-antibodies. The various antibody reactions employed in vitro do not reveal the mode of action of the antibodies in vivo. In cases with a positive Coombs' test, but no free antibodies in the serum, there may be violent hemolysis in vivo, but how the coated red cells are destroyed in the organism has not been clarified. In cases with free red cell agglutinins in the serum, it is not known why the substances, detectable in vitro as hemagglutinins, act as hemolysins in vivo. Furthermore, even in cases

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in which substances acting as hemolysins *in vitro* are demonstrable, it is not known whether these substances are the direct cause of red cell destruction *in vivo*. There is strong evidence in favor of the concept that the living organism actively participates in the red cell destruction, not only by production of antibodies, but by other means as well (6, 7). The spleen, for instance, probably plays two different rôles in immuno-hemolytic anemia. At least in some cases it produces auto-antibodies (4), but it also destroys red cells which have been affected by antibodies. After splenectomy, clinical improvement and decreasing red cell destruction is sometimes obvious, even when no change in the antibody titer has occurred (5). It would be of interest to learn the fate of the red cells coated with antibodies *in vivo*, also factors in the living organism which destroy these cells and, moreover, whether there are factors which inhibit hemolysis *in vivo*.

The discrepancy between the effect of a certain amount of antibody *in vitro* and *in vivo* is obvious in experimental hemolytic anemia. Muir and MacNee (8), in 1911, were the first to point out that a given amount of antibody hemolyzes more red corpuscles *in vivo* than *in vitro*. Two years later this observation was confirmed by Banti (9). He distinguished two phases in hemolysis after injection of red cell antibodies into animals. The first phase occurred immediately after the injection and slow hemolysis followed over a period of several days. In their experiments on guinea pigs, Dameshek and Schwartz (1) found the effect of immune antibodies to be stronger *in vivo* than *in vitro*. Wasastjerna (7) made a similar observation. He found that the enhanced and prolonged hemolytic effect *in vivo* was characteristic of immune antibodies, whereas saponin and streptolysin 0 destroyed more corpuscles *in vitro* than *in vivo*. There may exist a number of mechanisms which are responsible for the red cell destruction *in vivo* after injection of anti-red cell serum. Intra-vascular agglutination of red cells is probably one of them, because most immune sera used have a higher agglutinin titer than hemolysin titer *in vitro*. The importance of this mechanism has been stressed by Ham and Castle in 1940 (10). They found that the agglutinin concanavalin A caused hemolysis when injected into animals. Their finding was later confirmed by Dameshek and Miller (11). As early as 1902, Kraus and Sternberg (12) reported agglutination of whole blood taken from experimental animals given injections of anti-red cell serum. Identical observations have since been reported by Bessis and Freixa (13), and by Wasastjerna (7). Studies of the intravascular blood stream in experimental hemolytic anemia were made by Day and Perry (14), and by Wasastjerna (7), who found that there was a marked aggregation of red cells in the vessels. The magnifications used were low, however, and the technics not quite satisfactory. In consequence, the observations were not detailed enough. Therefore renewed detailed studies of intravascular agglutination in experimental immuno-hemolytic anemia with improved technics were necessitated.

Methods.

A simple and adequate technic for intravascular observation has been described by Fulton, Jackson and Lutz (15). They studied the blood vessels of the

transilluminated hamster cheek pouch with an ordinary microscope equipped with water immersion objectives. With the assistance of these investigators, this method was used in the present studies and found highly satisfactory. A monocular microscope equipped with a $10\times$ dry objective and a $50\times$ water immersion objective was employed. The oculars were: a $7.5\times$ micrometer ocular, a $10\times$ and a $20\times$ ordinary ocular and a $15\times$ wide field ocular. The magnifications thus obtained varied between 75 and $1,000\times$.

Six to ten-week-old male hamsters (*mesocricetus auratus*) were used for the experiments. They were anesthetized with nembutal intraperitoneally, about 0.2 cc of a 5 per cent solution to a hamster of 100 g. The cheek pouch was stretched out on a plastic block, immersed in warm Ringer solution, and observed under the microscope.

Anti-hamster red cell serum was prepared by repeated intravenous injections of washed hamster erythrocytes into a rabbit; the serum was inactivated and frozen. A two-fold dilution series was made up for titration of the hemolytic power of the serum: 0.2 cc of fresh guinea pig serum, diluted 1 : 10, and 0.2 cc of a 2 per cent hamster red cell suspension were added to 0.2 cc of serum dilution. The agglutinin titer was determined in the same way, but saline was used instead of complement. The titer was read after incubation of one hour at 37°C , and expressed as the final dilution of serum in the last tube showing agglutination or hemolysis. The agglutinin titer of the serum used was 1 : 768, and the hemolysin titer 1 : 384. This dilution resulted in complete hemolysis; barely visible hemolysis developed at a titer of 1 : 6144.

All hamsters were given injections of undiluted immune serum. The doses varied between 0.1 and 0.5 cc per 100 g body weight, administered once only, or once daily for two, three or four days — intraperitoneally, intravenously, or intracardially.

Blood for the counts was obtained from a small blood vessel on a paw of the hamster, incised using a sharp blade. Red cell counts were made in all cases, and reticulocyte counts in eight hamsters treated with immune serum. Dry smears on cover slips stained with cresyl blue were used for the reticulocyte count.

Results.

Five untreated healthy hamsters were observed. No red cell agglutination was seen in the blood vessels. For control two hamsters were given injections of normal rabbit serum: one of them was given 0.5 cc per 100 g body weight intracardially once only; the second one was given daily intraperitoneal injections of 0.25 cc per 100 g over a period of four days. The blood flow was completely normal, and no intravascular clumping of red cells was observed. Citrated blood showed no macroscopic or microscopic agglutination of red cells in vitro. The red cell count and the reticulocyte level did not change significantly during the period of observation.

Immune serum was given to 24 hamsters. As already mentioned, the dose and route of administration varied, but all doses were sufficiently large to bring about

a fall in the red cell count of over one million per cu.mm. The R. B. C. varied between 6.05 and 10.31 million in the untreated animals, average 8.1 million per cu.mm. The lowest R. B. C. recorded after treatment was 1.98 m. The mean of the lowest values in all animals treated was 4.3 and the average drop, due to the treatment, 3.8 million. The red cell count generally decreased over a period of three or four days after the last injection, after which a rise usually occurred.

Only four animals died after the injections. The cause of death was accidental in two cases: one animal was given too large a dose of anesthesia, and another inhaled Ringer solution during the microscopic observations. Death was thus attributable to the serum injections in two cases only. One of the animals died two days after the last intraperitoneal injection and the second one six days after an intracardial injection. The general condition of most of the hamsters was only slightly affected by the injections. The animals generally looked quite healthy, even when severe anemia occurred.

The mean initial reticulocyte value in eight hamsters was 3.5 per cent, and after the injections there was a rise to an average of 27.3 per cent. The highest reticulocyte peak noted was 68 per cent on the fourth day after the last injection in a course of 0.15 cc immune serum per 100 g daily over a period of four days. All animals treated developed a marked, transient, micro-spherocytic blood picture after the injections.

A drop of blood was taken from 15 animals and mixed with a small drop of 3.6 per cent sodium citrate solution on a glass slide, and studied macro- and microscopically at room temperature. In 13 of the 15 cases red cell agglutination was seen on the slide after treatment of the animal, never before treatment. The clumping was definitely agglutination, and not rouleaux formation, but the clumps were of moderate size and visible macroscopically in only two cases.

All of the 24 hamsters given injections of anti-hamster red cell serum revealed agglutination of the erythrocytes in the cheek pouch vessels. The phenomenon was recorded on a Kodachrome motion picture film (16). The degree of intravascular agglutination varied greatly, and in general it was found to be correlated to the doses of serum — or even more directly to the degree of anemia which followed upon the injections. It was not, however, the result of the anemia, since it appeared immediately after an injection into the blood, at a time when the red cell count had not had time to change. In one case the microscopic observations were started seven minutes after an intracardial injection. Marked intravascular agglutination of the red cells was seen. On the following day the amount of free cells in the vessels had increased again, but numerous cell clumps were still seen in the venules, and these clumps looked firmer than those observed immediately after the injection. Two days after the injection, intravascular red cell agglutination was still marked, probably more so than on the previous day, but four days after the injection there were occasional clumps in a few veins only, whereas in most vessels all cells were free. The intravascular agglutination generally lasted about four days after the last injection and disappeared when the anemia was most pronounced.

If clumping was moderate, it was visible only in some venules, usually in those with a slow flow, but sometimes also in larger veins draining blood from venules with slow flow. Hence the agglutination did not, probably, retard the flow, but the red cells had more time to become agglutinated in those vessels with slow flow. The arterial flow was generally normal in cases with mild agglutination in the veins. The red cells passed in single file in the capillaries.

Even when extensive clumping occurred, the difference between the number and size of clumps in the different veins was remarkable. All red cells were stuck together only in a very small number of vessels with flowing blood. The blood stream in treated animals generally consisted of a mixture of clumps of varying size, and of free cells. Most cells were clumped together in some of the veins, and a few cells were free. In others, again, most cells were free, and only occasional clumps were seen. In one and the same field there might be a vein in which the large clumps were in the majority, and another one of the same size and the same rate of flow in which all or almost all cells were free. When the vessels then were studied in backward direction, it was always found that in the small venules, forming the vein with large clumps, the flow was slower than in those forming the other vein.

In a very few instances, small clumps of agglutinated cells were seen in the capillaries. As a rule the cells passed through the capillaries in single file, even in cases with very marked agglutination in the venules. In these cases, the rouleaux-like files in the capillaries seemed, however, to be longer than in the untreated animals. The cells stuck together in the venules, particularly if the rate of blood flow was slow. Furthermore, the clumps in the various small venules were often seen to stick together when they passed into larger venules and met clumps from other parts of the venous tree.

The size of the clumps varied greatly. The smallest red cell clumps consisted of a few cells only, and measured about 10 micra in diameter. Numerous clumps of about 30—50 micra in diameter were seen in most animals treated, but sometimes the cells formed cylinder-like clumps which filled the entire diameter of the vessel; sometimes they were much longer than the vessel diameter, *i. e.* 200 or 300 micra. When these long clumps passed into larger veins with rapid flow, they always disintegrated. Short cylindrical clumps either broke up or changed shape becoming more or less spherical when passing into larger veins.

Definite clumps were seen in arterioles. They were always small, however, and even when the venules contained mostly large clumps, the majority of the cells in the arterioles were usually free.

There is only one plausible explanation of the difference in appearance presented by the venous and the arterial flow: most of the large clumps formed in the venules probably become broken up somewhere in the circulation, before the cells come out into the arterioles. The fact that clumps were hardly ever seen in the capillaries is explainable in the same way. That intravascular agglutination was a reversible phenomenon, was actually observed, particularly in the venous network where the blood sometimes passes from larger veins into smaller ones. The clumps broke up in these spots, or changed shape in order to enable them to

continue their passage. If the clumps were large and the passages narrow, then the blood stream sometimes stopped for a moment. Sooner or later they broke up, however, or changed shape so as to fit into the smaller vessels. No permanent plugging of vessels was seen in the venous network, arterioles, or capillaries. Static blood was sometimes seen in a few vessels of untreated animals, and there were often rather large areas of vessels with static blood in the animals injected, but the flow was never permanently stopped. When the study covered a period of sufficient length, then the blood was always seen to start circulating again. Thrombus formation was never observed.

Comment.

In the experiments described above, the doses of anti-erythrocyte serum were large enough to induce marked anemia, but not, as a rule, to kill the animals. Unquestionable intravascular red cell agglutination was seen in all animals treated, and there was no agglutination in the controls. Numerous venules in some of the hamsters were filled with large clumps, yet the circulation was not stopped. The animals were still in good general condition when observed, and most of them recovered from the anemia. The intravascular clumps often looked quite firm, yet plugging of vessels was never seen because the circulation forced the clumps to break up when the blood was due to pass through narrow passages. The reversibility of the intravascular agglutination may explain the satisfactory general condition of the animals, also the fact that the circulation was not much impaired.

The results of the present work confirm the finding of intravascular red cell agglutination in experimental hemolytic anemia, previously made by means of less satisfactory technics (7, 14). The «sludged blood» which Knisely et al. (17, 18) produced in experimental animals, with methods differing completely from those used in the present investigation, probably looked very similar in many respects. However, some divergencies may be mentioned. For instance, in our experiments, red cell clumps were never seen to plug vessels, and the difference between the clumping in the various vessels was probably more prominent than in Knisely's animals with «sludged blood». On no occasion did we observe «all the animals' blood changing to a thick muck-like sludge» as in Knisely's malaria-infected monkeys (19). The red cell clumps, found in the present investigation, were probably almost as friable as the groups of hamster red cells, described by Lutz et al. in infection, neoplasia, after trauma, and irradiation (20, 21, 22).

It has now been proved that injection of anti-erythrocyte serum into animals may cause marked intravascular red cell agglutination. However, this work was done with one serum only. Hence we do not know whether intravascular agglutination of red cells takes place regularly in experimental immuno-hemolytic anemia. It probably does so in most cases and with a large number of sera, because the agglutinin titer of the immune serum used in the majority of experiments reported (1, 7), was considerably higher than the hemolysin titer. The agglutination titer of the serum used in our experiments was lower than the end point

hemolysis titer, and only slightly higher than the total hemolysis titer. Even this serum caused a spectacular agglutination of the red cells in the vessels. Intravascular red cell agglutination thus probably occurs in all, or in most of the cases of experimental immuno-hemolytic anemia. It may be a regular phenomenon, but its significance has not been fully elucidated. The results of the present observations do not show whether red cell agglutination is required for development of anemia in animals injected with immune serum.

Ham and Castle (10, 23) have demonstrated that pure agglutinins may cause hemolysis *in vivo*. It is therefore quite probable that the intravascular agglutination of red cells following injection of immune serum is an important phase in the hemolytic process in the animal. Wasastjerna's (7) observations favor this concept, *i. e.* that the effect of pure hemolysins *in vivo* per hemolytic unit is much weaker than of immune serum, and that the former substances act for a much shorter period *in vivo* than does the serum. Young et al. (24) and Wasastjerna (7) have found evidence of the presence of a factor in fresh plasma which enhances agglutination of red cells. Ham and Castle (10) postulate that agglutinated red cells are destroyed in the circulation because of their greater susceptibility to mechanical trauma than that of free cells, and because red cell clumps are sequestered in the spleen and other organs containing static blood. Even if the agglutination is reversible, there must be a considerable traumatic action on the cells every time the clumps have to break up.

From the experiments now presented it may be concluded that a high degree of intravascular agglutination, caused by immune agglutinins, is compatible with life and recovery, and does not markedly affect the general condition. This finding permits the postulation that intravascular agglutination may also occur in immuno-hemolytic anemia in man, without causing extensive plugging of blood vessels and immediate death. As a matter of fact, Zilliaens and Arajärvi (25) have noted intravascular clumping in the conjunctival vessels of infants suffering from erythroblastosis fetalis, and Wasastjerna et al. (26) in adults with acquired hemolytic anemia.

Intravascular red cell agglutination is probably an important phase in the development of experimental immuno-hemolytic anemia, but is not by any means the only mechanism which destroys erythrocytes. There is probably also a direct effect of antibody and complement, and possibly the very fact that the red cells are coated with antibody renders them susceptible to destruction *in vivo*. Young et al. (24) produced several different kinds of immune-iso-antibodies active against dog red cells. The most pronounced hemolytic effect *in vivo* was obtained with the one which coats and lyses cells *in vitro*. Phagocytosis of the red cells is another important mechanism which destroys red cells in animals given injections of anti-erythrocyte serum (27). In immuno-hemolytic anemia in man there probably are similar mechanisms which destroy the red cells. Not mentioned in the discussion above is fragmentation of red cells which probably occurs in some hemolytic disorders (6). Fragmentation was not observed in our intravascular studies of animals.

Summary.

Anti-erythrocyte immune serum was injected into hamsters in doses large enough to cause hemolytic anemia, but not, as a rule, to kill them. The blood vessels of the cheek pouch were studied under the microscope. Intravascular red cell agglutination was seen in all animals treated, but in none of the controls.

The following characteristics of intravascular red cell agglutination were observed: The red cells generally passed the capillaries in single file; only occasional small clumps of cells were seen. Most red cells in the arterioles were free, but in numerous arterioles there were small clumps. Usually, the venous blood consisted of a mixture of free cells and red cell clumps, varying in size. The degree of agglutination varied markedly in the different venules of the same cheek pouch; some venules contained mainly large clumps, and in some the majority of erythrocytes were free. Single cells passing through capillaries stuck together on entering venules with a slow flow. The intravascular red cell agglutination was reversible, and plugging of vessels was not observed.

Intravascular red cell agglutination is probably one of several mechanisms responsible for the red cell destruction in experimental immuno-hemolytic anemia.

References.

1. Dameshek, W. and Schwartz, S. O.: Hemolysins as the cause of clinical and experimental hemolytic anemias with particular reference to nature of spherocytosis and increased fragility. *Am. J. Med. Sc.* 196: 769, 1938. — 2. Dameshek, W. and Schwartz, S. O.: Acute hemolytic anemia (acquired hemolytic icterus, acute type). *Medicine* 19: 231, 1940. — 3. Boorman, K. E., Dodd, B. E. and Loutit, D. M.: Hemolytic icterus, congenital and acquired. *Lancet* 1946, p. 812. — 4. Dameshek, W.: Acquired hemolytic anemia. *Physiopathology with particular reference to autoimmunization and therapy. The 1950 Proceedings of the International Society of Hematology*, p. 120. — 5. Dacic, J. V. and de Gruchy, G. C.: Auto-antibodies in acquired haemolytic anaemia. *J. Clin. Path.* 4: 253, 1951. — 6. Heilmeyer, L.: Die Hämolytischen Anämien. *Sang* 21: 105, 1950. — 7. Wasastjerna, C.: The destruction of red blood corpuscles in experimental hemolytic anaemia. *Acta Med. Scand., Suppl.* 258, 1951. — 8. Muir, R. and Mac Nee, J. W.: The anemia produced by a hemolytic serum. *J. Path. Bact.* 16: 410, 1911. — 9. Banti, G.: Splénomégalie hémolytique anhémoïétique; le rôle de la rate dans l'hémolyse. *Sem. Méd.* 33: 313, 1913. — 10. Ham, T. H. and Castle, W. B.: Relation of increased hypotonic fragility and of erythrostasis to the mechanism of hemolysis in certain anemias. *Tr. A. Am. Phys.* 55: 127, 1940. — 11. Dameshek, W. and Miller, E. B.: Pathogenetic mechanisms in hemolytic anemias. *Arch. Int. Med.* 72: 1, 1943. — 12. Kraus, R. and Sternberg, C.: Über Wirkungen der Hämolyse im Organismus. *Centralbl. f. Bakt.* 32: 903, 1902. — 13. Bessis, M. and Freixa, P.: Etudes sur l'ictère hémolytique expérimentale par injection et ingestion d'antiserum. *Rev. d'hémat.* 2: 114, 1947. — 14. Day, R. and Perry, E.: Intravascular hemagglutination. Experimental and clinical observations with special reference to the pathogenesis of kernicterus. *Blood* 5: 1114, 1950. — 15. Fulton, G. P., Jackson, R. G. and Lutz, B. R.: The use of the cheek pouch of the hamster, *Cricetus auratus*, for the cinephotomicroscopy of small blood vessels. *Anat. Rec.* 96: 554, 1946. — 16. Wasastjerna, C., Dameshek, W. and Joffes, D. L.: Intravascular agglutination of red cells in hamster cheek pouch using immune anti-erythrocyte serum. Motion picture film,

Figs. 1—4. Intravascular agglutination of red cells after injection of anti-erythrocyte serum. The photographs have been enlarged from a 35 mm Kodachrome motion picture film (16).

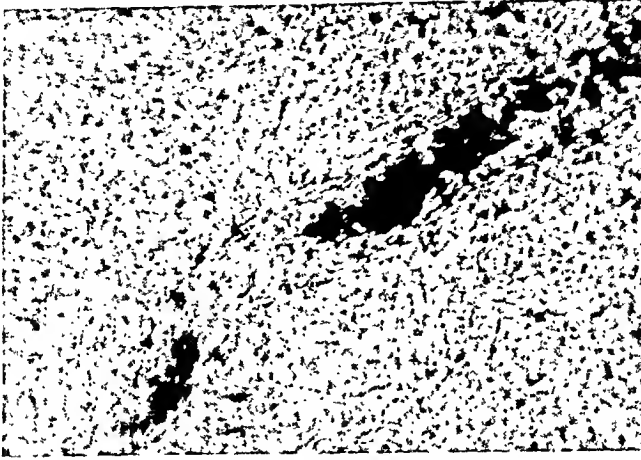


Fig. 1. Venule in an anemic animal. R. B. C. reduced from 7.5 to 2.2 million. $\times 200$.

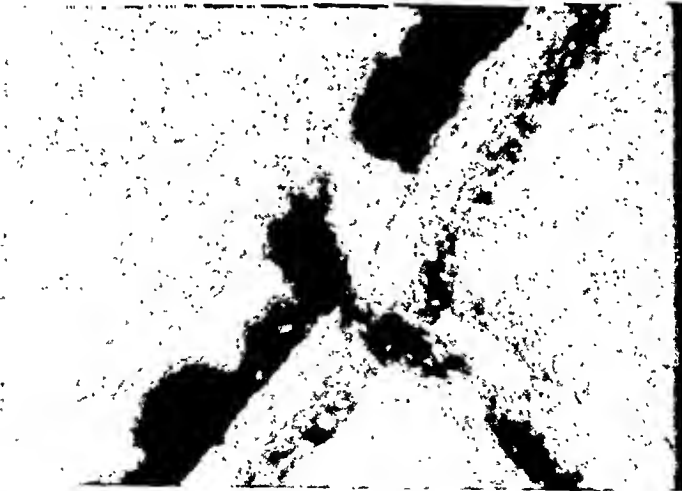


Fig. 2. Venule containing large red cell clumps. $\times 200$.

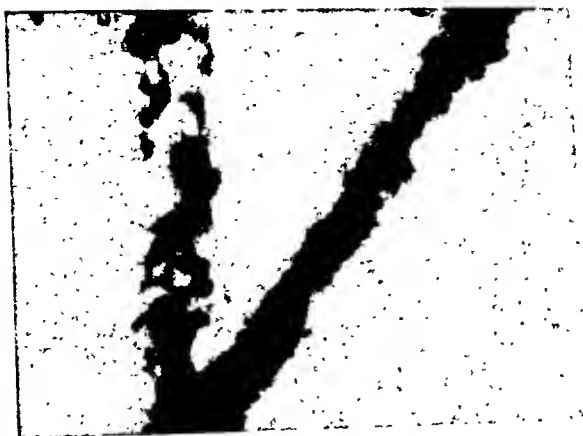


Fig. 3.



Fig. 4.

Fig. 3 & 4. Marked agglutination of red cells in the venules and fine granularity in the arterioles.

- Boston 1952. — 17. Knisely, M. H., Bloch, E. H., Eliot, T. S. and Warner, L.: Sludged blood. *Science* 106: 431, 1947. — 18. Knisely, M. H.: An annotated bibliography on sludged blood. *Postgraduate Medicine* 10: 15, 1951. — 19. Knisely, M. H., Stratman, W. K., Eliot, T. S. and Bloch, E. H.: Knowlesi malaria in monkeys. *J. National Malaria Soc.* 4: 285, 1945. — 20. Lutz, B. R., Fulton, G. P. and Akers, R. P.: Circulation in membranes of the frog and hamster after stasis, trauma and under pathological conditions. *Fed. Proc.* 9: 81, 1950. — 21. Lutz, B. R., Fulton, G. P. and Akers, R. P.: White thromboembolism in the hamster cheek pouch after trauma, infection and neoplasia. *Circulation* 3: 339, 1951. — 22. Fulton, G. P., Lutz, B. R., Jofte, D. L. and Maynard, F. W.: Effects of beta and X-irradiation on circulation in hamster cheek pouch. *Fed. Proc.* 11, No. 1, 1952. — 23. Castle, W. B., Ham, T. H. and Shen, S. C.: Observations on the mechanism of hemolytic transfusion reactions occurring without demonstrable hemolysis. *Tr. A. Am. Phys.* 63: 161, 1950. — 24. Young, L. E., O'Brien, W. A., Miller, G., Swisher, S. N., Ervin, D. M., Christian, R. M. and Yuile, C. L.: Erythrocyte-isoantibody reactions in dogs. *Tr. N. Y. Acad. Sci.* 6: 209, 1951. — 25. Zilliacus, H. and Arajärvi, T.: Intravascular red cell aggregation in erythroblastosis fetalis. *Acta Paed.* 41: 267, 1952. — 26. Wasastjerna, C., Dameshek, W., and Komninos, Z.: Direct observations of intravascular agglutination of red cells in acquired auto-immune hemolytic anemia. In press. — 27. Baumgartner, W.: Experimentelle hämolytische Anämie. *Helv. Med. Acta* 14: 502, 1947.
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Some Observations Concerning the L. E. Phenomenon.

By

M. C. VERLOOP, M. D.

(Submitted for publication September 3, 1953).

In January, 1948, Hargraves, Richmond and Morton published an article in the *Proceedings of the Mayo Clinic*, in which they reported on a particular kind of cell, found in the bone marrow of patients suffering from lupus erythematosus. Many publications have since appeared on these so-called L. E. cells, and thus the clinical picture of lupus erythematosus has become a matter of general interest. As early as 1872, Kaposi distinguished two types:

- (1) The discoid type, characterized by a chronic benign course, mainly occurring at an advanced age and confined to cutaneous changes.
- (2) The disseminated type, with an acute feverish course or chronic recurrence, often with a fatal issue, usually occurring in the younger age groups, with a predilection for women. As regards diagnosis, treatment and prognosis the best thing one can do is to keep these two forms apart, although the chronic discoid form may change into the disseminated type.

Table I shows the variety of the clinical picture of generalised lupus erythematosus in 8 patients observed over the last two years. Ages of the patients were: 35, 50, 55, 56, 57, 57, 63 and 68 years, 6 were women and 2 men.

Table 1.
Generalised lupus erythematosus.

Fever	7	Lymphadenopathy	3
Arthritis	8	Cutaneous features	4
Albuminuria	7	Mucosal symptoms	1
Elevat. sed. rate	8	Peri-(Myo-)carditis	2
Anemia	8	Pleurisy	5
Loss of weight	6	Psychic disturbances	2
Leukopenia	4		

It is an highly variable picture, and the diagnosis may be difficult to establish. In 1948 characteristic cells in blood and bone marrow were found by means of a fairly simple technique. This method soon proved to be an important aid to diagnosis.

Hargraves and his collaborators described, in heparinized bone-marrow of patients with disseminated lupus erythematosus, a particular cell which they called the L. E. cell. It was almost always a polymorphonuclear leucocyte with a round inclusion body, which showed a cloudy homogenous structure with no clear chromatin pattern (Fig. 1—3). Sometimes this inclusion body was completely within the cell, sometimes still partially outside it. Special staining for chromatin showed that this inclusion body consisted also of nuclear material. This nuclear material was evidently largely dissolved, so that it stained red instead of violet-red. Sometimes two polymorphonuclear leucocytes were observed, which were trying to phagocytize a rose-coloured homogenous nuclear mass (fig. 4); this was especially clearly visible in the phase-contrast microscope. Between the cells there were always swollen nuclei, forming exactly the same homogeneous structureless mass as the phagocytized material (Fig. 5). When dealing with these extracellular masses often surrounded by leucocytes or monocytes, we sometimes speak of the L. E. phenomenon.

Hargraves et al. further described a second cell, also characterized by a second nucleus in the protoplasm. They were usually so-called reticulum cells, but sometimes also polymorphonuclear leucocytes. This second nucleus, which might be phagocytized or which might have been formed in the cell itself by nuclear division, still showed the chromatin structure. These so-called "start cells" were found in the bone marrow of patients with all kinds of diseases and were not specific for these diseases.

Hargraves always emphasized the importance of the phenomenon of lysis, i. e. the loss of the nuclear structure, for the formation of the L. E. cells. First lysis occurred and later phagocytosis. Although some investigators assume that the phagocytized nuclear material originates from lymphocytes, others observed that the nuclei of polymorphonuclear leucocytes swelled and were subsequently phagocytized. I personally observed the latter. This phenomenon is therefore quite different from the phagocytosis of a more or less intact cell or cell nucleus, in which pyknosis of the nuclear material is often observed. It is also different from the degeneration of older cells, in which the formation of conglomerations is observed in the smear, with a thready chromatin structure. One should also not confuse the L. E. cells with the so-called bare nuclei in the smears. In the L. E. phenomenon a homogeneous mass without nuclear structure is observed, staining by the May—Grünwald—Giemsa method, and situated intra- or extracellularly. It was soon apparent that the L. E. cells could also be demonstrated in venous blood from cases of generalized lupus erythematosus, when the blood — after having been made incoagulable — was centrifuged and smears were made of the leucocyte layer. Since that time a multitude of publications on L. E. cells have appeared.

Haseriek found that the gamma globulin of the plasma of patients with disseminated L. E. contains a factor with an antigenic nature, which causes the L. E. phenomenon. When plasma of these patients is added to normal bone marrow or leucocytes, L. E. cells develop. The problem as to whether the L. E. phenomenon is specific for disseminated lupus erythematosus, is of course of great

importance. It appears to be not quite specific. It has occasionally been described in diseases such as leukemia and myelomatosis. Another finding of Haserick was that addition of certain fungi to plasma may give rise to the L. E. plasma factor. Inderbitzin observed, in blood of normal people made incoagulable with liquoid (Roche), increased phagocytosis of nuclear material after centrifugation, by which the leucocytes could assume a marked resemblance to L. E. cells. In the beginning of 1953 Walsh and Zimmerman also Inderbitzin reported on the formation of the L. E. cells in the bone marrow of three patients with severe hypersensitivity reactions after administration of penicillin.

We observed lysis of nuclear material and attempts at phagocytosis of the material in a patient with a generalized scleroderma (Figs. 6, 7).

We must still be careful in drawing conclusions. It is possible that there was a concurrent disseminated lupus erythematosus in a number of these patients. The question arises as to whether the cellular changes found had indeed the typical L. E. structure. In recent years the L. E. cell has been looked for in numerous diseases, and it has been proved that the formation of L. E. cells in vitro may be considered to be almost specific for lupus erythematosus.

Hargraves discovered these cells because in his laboratory heparinized bone marrow was centrifuged and smears made of it as a routine procedure. After his discovery it was thought that the anticoagulants were necessary to the production of the cells. It appeared afterwards that L. E. cells were also present in defibrinated blood (Eppes) and in the blood clot after centrifugation. Could it be that mechanical damage to the cells is the cause of the lysis of the cells and nuclei with subsequent phagocytosis?

In my opinion, at present we may imagine the process as follows. Leucocytes are sensitized under the influence of the plasma factor, perhaps in the same manner as erythrocytes are sensitized in acquired hemolytic anemia. In vivo usually nothing happens, but no sooner do the leucocytes enter a suitable milieu (in which perhaps a second necessary factor arises), lysis of cells and swelling of cellular nuclei occur, followed by phagocytosis. This might again be comparable to some extent with the increased phagocytosis of sensitized erythrocytes in opsonin tests in acquired hemolytic anemia.

At present Hargraves (P. A. O'Leary) feels that the blood platelets perhaps constitute the second factor in the development of the L. E. cells. When blood is taken from a patient, there will always be some damage to the platelets and material is liberated from these. When we compare various techniques, it strikes us that the smallest number of L. E. cells is found when the blood is treated as carefully as possible and the smears are also made as quickly as possible. Hargraves assumes that liberated material from damaged blood platelets might cause the formation of the L. E. cells. This is one of the reasons why during the past eighteen months he has used another technique to find L. E. cells. He first allows the blood to coagulate, and then forces the clot through a filter after 1.5—2 hours, and centrifuges the red liquid. Smears are then made of the cell layer obtained (see also Gougea and Magath). He obtained better results with this method than with other ones, which were usually based on rendering the blood

ineoagulable. We also used this blood coagulation method during the past months with the following results:

Table 2.

Three methods used in demonstrating the L. E. cell phenomenon in venous blood.

1. Oxalated blood 10' at room temperature; 15' centrifuged at 2,000 r. p. m.; films are made of the "Buffy coat" (Holman).
2. Oxalated blood 30' at room temperature; 30' at 37° C; 3' centrifuged at 2,000 r. p. m.; films are made (Mathis).
3. Blood is allowed to coagulate at room temperature for two hours; the clot is expressed through a screen; the bloody liquor is centrifuged for 5'; films are made (Magath).

Table 3.

Authors examination of venous blood for L. E. cells.

	Number of L. E. cells per 1,000 polymorph. count in Oxal. blood; room temp.	Number of L. E. cells per 1,000 polymorph. count in Oxal. blood; 37° C.	Number of L. E. cells per 1,000 polymorph. count in the two-hour blood clot.
v. B., female 68 yrs	0	1	16
O., female 35 yrs	0	0	67
Tw., female 57 yrs	0	0	4
R., female 57 yrs	0	3	73
K., male 55 yrs	0	0	8

I also compared slides of the bone marrow made incoagulable, as Hargraves had done, with preparations of pressed-out blood-clots in the same patients. The number of L. E. cells found in the clots of venous blood appeared to be much larger. Often the examination of the bone-marrow slides was negative. It seems no longer necessary to have a sternal puncture done to look for L. E. cells in patients suspected of having disseminated lupus erythematosus.

The study of the preparations of these pressed-out blood clots is undeniably more difficult than of blood made incoagulable. There are many defective cells and cell clusters and vacuolization in the smears. However, the gain in positive cases is so great and the method so simple, that we must accept the drawbacks. This method of examining the blood clot after two hours is a great asset for the making of a diagnosis. The method is sometimes also negative, however, while disseminated lupus erythematosus still exists. This is not so very remarkable when we realize how varied is the picture of lupus erythematosus. The best chance of finding the L. E. phenomenon exists during a crisis of this disease. It is sometimes necessary to repeat the examination for L. E. cells several times in patients suspected of this disease, before positive results are found.

Summary.

The importance of the finding of the L. E. cell for the diagnosis of disseminated lupus erythematosus is discussed. By the author three methods for demonstrating of the L. E. cell were compared. The blood-clot method of venous blood gave the best results and is a great asset for the making of the diagnosis.

References.

1. Hargraves, M. M., a. o.: Proc. Staff. Meet. of the Mayo Clinic. 1948, 23, 25. —
 2. Haserick, J. R., a. o.: Amer. J. Med. Sc. 1950, 219, 660. — 3. Haserick, J. R. and Lewis, L. A.: Blood 1950, 5, 718. — 4. Inderbitzin, Th.: Schweiz. Med. W.schrift: 1951, 81, 1298. — 5. Inderbitzin, Th.: Schweiz. Med. W.schrift: 1952, 82, 561. — 6. Walsh, J. R. and Zimmerman, H. J.: Blood, 1953, 8, 65. — 7. Inderbitzin, Th.: Aeta haemat. 10, 31, 1953. — 8. Eppes, W. and Ludovia, E.: Blood 1951, 6, 466. — 9. O'Leary, P. A.: Proc. Staff. Meet. of the Mayo Clin. 1952, 27, 409. — 10. Gougea, L. M., a. o.: J. Invest. dermat.: 1950, 15, 11. — 11. Magath, T. B. and Winkle, V.: Amer. J. Clin. Path. 22, 556, 1952. — 12. Holman, S.: J. Clin. Path. 1951. 4, 290. — 13. Mathis, H. B.: Blood, 1951, 6, 470.
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Fig. 1. Two polynuclear cells with inclusion bodies. L. E. cells in the peripheral blood.

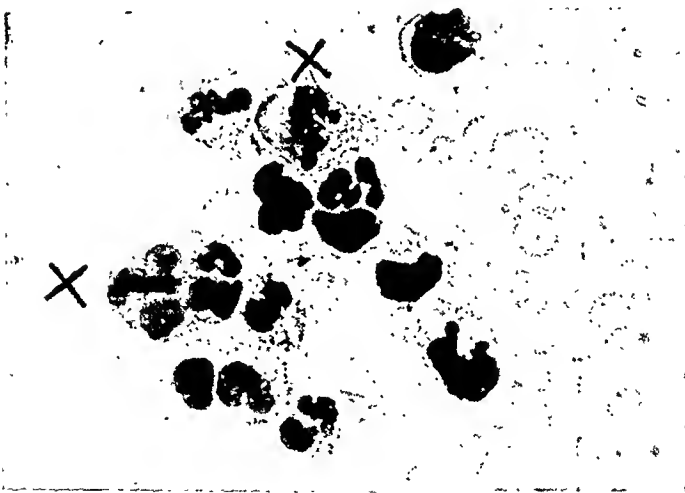


Fig. 2. Cluster of leucocytes; beside the marks are seen typical L. E. cells (peripheral blood).

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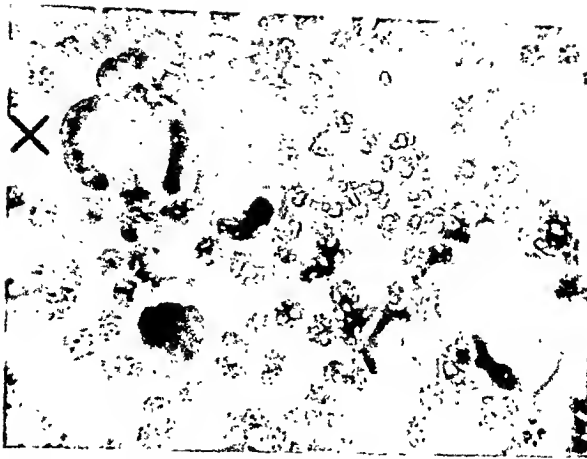


Fig. 3. Beside the mark is seen a L. E. cell with a large inclusion body.

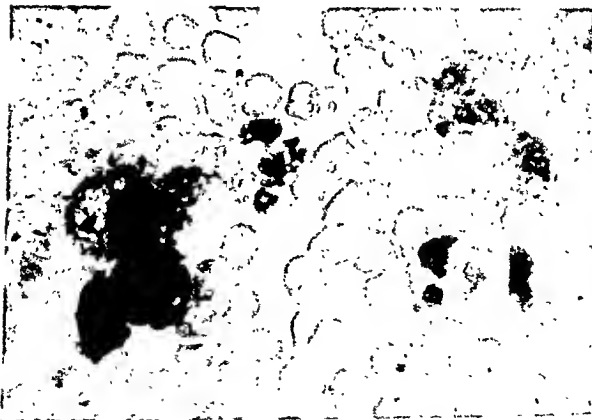


Fig. 4. Bone marrow slide with to the left a characteristic L. E. cell. To the right is a homogeneous mass lying in between two polynuclear leucocytes.

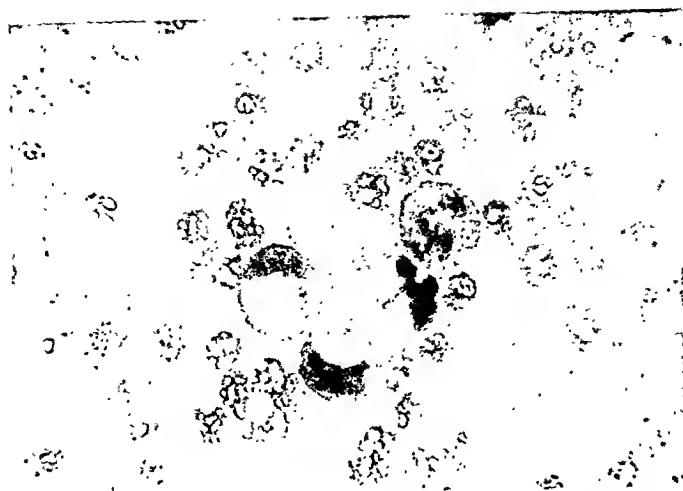


Fig. 5. Bone marrow showing partly intra-, partly extra-cellular nuclear masses. The L. E. phenomenon.

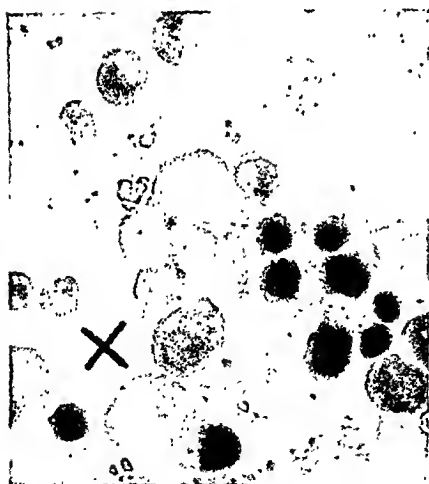


Fig. 6. Bone marrow of a patient with generalized scleroderma. Lysis of nuclear material.

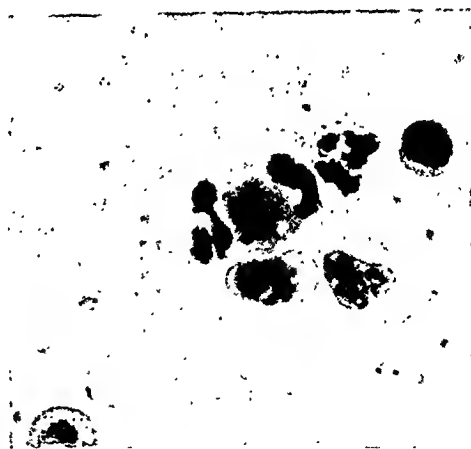


Fig. 7. Bone marrow of a patient with generalized scleroderma. A homogeneous nuclear mass lying in between two polynuclear leucocytes: the extra-cellular L. E. phenomenon.

From Medical Department B of the Rikshospital, Oslo. (Chief: Professor H. A. Salvesen, M. D.)

Pulmonary Fibrosis.

By

OLE JACOB BROCH, TORJUS MOE and MARGRETHE WEHN.

(Submitted for publication September 12, 1953.)

Patients with extensive bilateral pulmonary infiltrations of unknown character are frequently seen in medical departments and private practice. Pulmonary fibrosis is usually diagnosed, and even after years of observation the etiology will be obscure. In order, if possible, to gain a clearer concept of the pathogenesis, etiology and prognosis of these cases, we have collected those of them which were treated in this Department in the period 1940—1950.

Pulmonary fibrosis is the outcome of a pathological process which accompanies many diseases of the lungs and which may represent the final stage of some of them. The parenchyma is converted to connective tissue to a greater or less extent.

Spain (32) has examined post mortem 100 cases of *cor pulmonale*. He maintains that the fibrosis of the lungs develops first in the walls of the bronchi, and that the resulting emphysema induces vascular changes with pulmonary hypertension and *cor pulmonale*.

Any infection, chemical or mechanical irritants, and also radiological lesions may give rise to inflammatory processes resulting in a diffuse pulmonary fibrosis. There are also certain general systemic diseases which are occasionally combined with pulmonary fibrosis. In several of these the etiology remains obscure.

A bronchopneumonia provoked by ordinary microbes will occasionally lead to fibrosis. It has been maintained that the new antibiotics will be responsible for more frequent pulmonary fibrosis because bronchopneumonia is cured more frequently than it was before (7). Pneumococcal pneumonia seldom gives rise to fibrosis. Certain viri, the virus of influenza in particular, attack the interstitial tissue of the lungs and provoke fibrosis. In influenzal bronchopneumonia of only 9 to 10 days' duration there may already be a definite fibroblast reaction in the lungs, forming the starting point of a pulmonary fibrosis (3). We can now hardly doubt that extensive pulmonary lesions, with development of extensive interstitial pulmonary fibrosis, may follow virus infections with no other cause.

In some cases fungus infections give rise to extensive pulmonary lesions. *Coccidioidomycosis* is apt to be followed by permanent changes in the lungs such as bronchiectasis and fibrosis (42). *Histoplasmosis* of the lungs can resemble almost any other disease of the lungs. There is nothing characteristic about the radiological picture it presents (12). *Geotrichosis* can provoke a miliary infiltration of the lungs and present great diagnostic difficulties in respect of pulmonary fibrosis of unknown origin. Sundgaard and his associates (36) mention 4 cases of *geotrichosis* with miliary opacities. Reiersol (26) discusses the so-called «hemp diseases» or «mokkasjuken», as it has been called for many years in Norway. It occurs among workers on hemp, jute and linen, and it is due to an allergic reaction which obviously depends on both dust and fungi acting as antigens. A similar disease is discussed by Felson and his associates (6) in 12 renovators. The possibility of virus infection has been entertained. The ultimate effect of these diseases of the lungs is apt to be a permanent pulmonary fibrosis (Editorial foot note to the Yearbook of Medicine 1951, page 251).

The fibrosis following dust inhalation of a series of foreign bodies such as silica and asbestos is well known.

Several irritating gases and vapour from metals have gradually been found to be capable of provoking acute changes in the lungs, chemical pneumonitis and, in a certain number of cases, particularly in connection with beryllium, chronic diseases of the lungs. After several years' exposure to it, beryllium provokes pulmonary fibrosis with miliary or larger infiltrations of the lungs. Inhalation of cadmium gas over a long period seems to be capable of provoking chronic changes in the lungs, emphysema in particular. The so-called hard metals can give rise to chronic changes in the lungs resembling sarcoidosis from the radiological point of view (31). Sjöberg (31) maintains that the term «pneumoconiosis» should also include these cases of gas irritation of the lungs.

Radiological treatment may give rise to fibrous pulmonary changes.

Malignant tumors, both primary and metastatic, may be associated with fibrosis. Among others, Peabody jr. & al. (23) have described 3 cases of carcinoma metastases with varying degrees of fibroblastic proliferation. In the case of «alveol cell tumor» simultaneous and considerable fibrosis and thickening of interalveolar septa are described (14).

Several systemic diseases may occasionally be associated with pulmonary fibrosis — sarcoidosis Boeck, tuberosclerosis, lymphogranulomatosis and the so-called diffuse vascular or collagen diseases such as scleroderma, dermatomyositis, and lupus erythematosus disseminatus. Among these systemic diseases sarcoidosis is evidently paramount. The literature on the subject is enormous. Boeck's sarcoidosis is definitely no etiological nosological entity, but rather intrinsically an allergic reaction in response to a series of different harmful agents. We have never felt entitled to make this diagnosis on the evidence of the lung findings alone without histological support. The radiogram is by no means characteristic, but may resemble any form whatsoever of diffuse interstitial pulmonary fibrosis. It may also resemble among other things myomatosis with cyst-formation. Both conditions may show tuberculin anergy and changes in the bones. In our experience

Kveim's reaction is often not decisive. Nelson (19) regards Kveim's reaction not as specific but as a cutaneous reaction to various antigens in a person suffering from sarcoidosis, in other words, he takes it to be an isomorphic, foreign-body reaction.

Lastly, we would mention some special and little-known forms of interstitial pulmonary fibrosis.

Chronic diffuse myomatosis is characterized by numerous cysts lined by cubic or cylindrical epithelium and surrounded by connective tissue and much smooth muscle. Such lungs have also been called honeycomb lungs. The cysts develop as the result of the bronchial obstruction which is due to the progressive fibrosis followed by emphysema. Cyst-like clarifications can often be found in bones of the fingers. The appearance of a lung roentgenogram is characteristic, with net-shaped, fine stripes surrounding clarifications ranging in size from a pin's head to a pea. The resemblances to miliary tuberculosis, sarcoidosis Boeck, silicosis and carcinomatosis in patients suffering from tuberosclerosis have been described among others by de Fine Licht (15) and Samuelsen (29). Oswald and Parkinson (21) have studied 16 patients with thin-walled cysts in the lungs. Six patients between the ages of 7—24 years presented honeycomb lungs combined with spontaneous pneumothorax — a complication said to be relatively common. Von Stoessel (39) regarded the disease as a »muscular cirrhosis», maintaining that it was due to an interstitial inflammation with degeneration of the lung parenchyma.

A number of cases of interstitial pulmonary fibrosis with cystic changes have also been discussed in association with the so-called collagenic diseases. Pulmonary fibrosis in cases of scleroderma has been reported by several authors (2, 4, 33). Church & Ellis (2) have recorded 2 cases of scleroderma with cystic changes in the lungs as in honeycomb lungs. Sundin & Tomenius (37) have described a case of marked pulmonary fibrosis combined with scleroderma in the skin.

In 1944 Hamman & Rich (11) recorded 4 cases of a curious condition with progressive, diffuse fibrosis in the walls of the alveoli. They called this condition acute interstitial fibrosis. These authors entertained the possibility that this might be a virus infection. Up to 1948 a total of 6 cases of this disease had been described (23, 24).

Interstitial pneumonitis with deposits of cholesterol is described by Waddell and his associates (40). In the most advanced stages fairly marked fibrosis was found, with golden-yellow areas showing a high cholesterol content. Robins and his associates (27) have recorded 11 cases of chronic pneumonitis of the cholesterol type in which the lungs were intensely yellow in the early stages and presented in the later stages extensive interstitial pneumonitis. Parkinson (22) has recorded a case of honeycomb lungs with an eosinophil xanthomatous granuloma in the femur. Pulmonary fibrosis and cyst formation may be the only manifestations of this disease in its chronic form.

Rheumatic pneumonitis was described by Gouley in 1938 (9 a—9 b). He assumes that the changes in the lungs, which eventuate in an interstitial fibrosis, are due in the main to a relapsing rheumatic infection and, to a lesser degree, to the congestion caused by the mitral stenosis. The congestion promotes indeed, the

interstitial fibrosis, but is in his opinion of secondary importance. Gouley applied the term »stiffened honeycomb» to these lungs showing marked interstitial fibrosis. Pulmonary fibrosis in cases of mitral stenosis has been described by other authors (18). Seldin and his associates (30) have recorded 6 fatal cases of rheumatic pneumonitis. It is difficult to decide to what extent rheumatic pneumonitis gives rise to a chronic pulmonary fibrosis, and whether it is possible to distinguish it from the chronic congestion of the lung (21).

The symptoms of pulmonary fibrosis vary with the degree of the morbid processes and the location of the disease in the lungs. It is not rare for the extensive miliary and patchy opacities in both lungs to be discovered incidentally in the course of routine screening. The physical findings are, as a rule, modest. The symptoms are more influenced by the localization of the pulmonary fibrosis than by its degree (32). The localization of the pulmonary fibrosis in the interstitial tissue, particularly around the bronchi, gives rise to slight symptoms, any intra-alveolar fibrosis provoking functional disturbances which depend directly on the quantity of pulmonary tissue involved. Wright and Filley (43) say that pulmonary fibrosis is a comparatively benign process when there is no complicating diffuse emphysema. As a rule, these symptoms progress gradually during several years consisting of cough and dyspnea which increase when emphysema sets in. With signs of fully developed cor pulmonale, the disease is apt to progress rapidly and to end in death after a comparatively short interval.

Pulmonary fibrosis is capable of influencing the functions of respiration and circulation in many ways. Reduction of ventilation in certain parts can be compensated by hyperventilation in other parts. Lindskog (16) says that in cases of direct bronchial obstruction there develops an indirect peripheral pulmonary ventilation from those parts of the lung where the alveoli are ventilated over to the parts deprived of their air supply (collateral respiration). It is also possible for blood to be shunted from diseased to hyperventilated areas. Gray and his associates (10) have shown by catheterization of the heart that there is a collateral circulation between the bronchial and the pulmonary arteries.

The arterial oxygen saturation is reduced when pulmonary fibrosis is more extensive and when the lungs are emphysematous. Several observers (1, 25 and 38) have shown that oxygen saturation is reduced by pulmonary fibrosis and emphysema. Work effects a further reduction of this saturation. Storstein (34) has investigated the effect of inspiring pure oxygen on the circulation in various forms of anoxia. The anoxia of diseases of the heart and lungs should be dealt with before irreversible changes in the blood vessels set in. However, in cases of severe pulmonary insufficiency the administration of pure oxygen may prove harmful. Since the anoxia acts as a stimulus to the respiratory centres, and since this stimulus is removed by a supply of oxygen the patient suffers from hypoventilation with a consequent further increase of the carbonic acid tension. Wilson and his associates (41) have found that in cases of severe emphysema there is a considerable increase in the carbonic acid content of arterial blood after the administration of oxygen. The most rational treatment of these cases would be to combine a supply of oxygen with artificial respiration.

Own Investigations.

Our material consists of 54 cases of chronic pulmonary fibrosis of unknown origin seen in the 10-year period 1940—1950. To these may be added 23 cases in which sarcoidosis Boeck was diagnosed. The bilateral pulmonary changes in this disease cannot be radiologically distinguished from those of the other diseases. There were, however, 15 cases with simultaneous bilateral hilus adenitis. In all these cases the diagnosis was verified histologically by biopsy of a gland of the conjunctiva or of the skin. Of course it is conceivable that sarcoidosis may effect changes only in the lungs and in such cases a certain diagnosis is impossible without a lung biopsy.

All our patients were subjected to numerous bacteriological examinations of sputum with tubercle bacillus culture.

The age distribution of our cases was as follows:

	Men	Women
Under 20 years.....	1	0
20—30 "	2	4
30—40 "	4	5
40—50 "	6	5
50—60 "	7	9
Over 60 "	7	4
	<hr/> 27	<hr/> 27

A boy, born in 1932 who suffered from pneumonia with empyema when 4 years old. Since then he had suffered from cough and expectoration with progressive dyspnea. In 1941 bilateral pulmonary infiltration with clarifications was discovered. He had clubbed fingers, and he suffered constantly from bouts of fever, gradually becoming quite unfit for work. The radiological condition was approximately unchanged in 1947.

There can be no doubt that this was an ordinary case of bronchiectasis following pulmonary infiltration in childhood with considerable, bilateral fibrous changes in the lungs at the same time.

In 8 cases the patients stated that their illness had begun acutely with fever and symptoms suggestive of pneumonia or bronchopneumonia. In one case the onset of the disease was rather acute with pain in the chest and joints and a very high E. S. R. It is therefore possible that the disease in these cases had developed as a sequel to an acute infection of the lungs. We cannot however dismiss the possibility that the pulmonary fibrosis had developed before and independently of the acute infection which had merely drawn attention to this condition, the patient being inclined naturally enough to put the blame for his ills on the acute disease. These cases, supposed to have shown an acute onset did not differ in any way from the others in their clinical behaviour.

In altogether 19 cases there was a record of a previous attack of some pulmonary disease which may have been pneumonia. But in most of these cases this happened many years before the onset of the symptoms. In two cases there was a history of pleurisy.

The bacteriological examinations of the sputum showed the ordinary flora. In 19 cases green hemolytic streptococci were found several times. A positive cutaneous reaction to hemolytic streptococci was found in one of the five patients thus examined. In 5 cases various species of fungus were found without any etiological significance being attached to them. There was however, one case in which fungus infection deserves discussion:

A woman, born in 1921, caught a cold in August 1949. In September 1949 a radiogram showed scattered bilateral miliary opacities. Mantoux and Kveim negative. Anti-streptolysin titer: 110. Hemolytic streptococci and hemophilus influenzae in the sputum. No tubercle bacilli. E. S. R. constantly somewhat raised. Progress of the disease in December 1950. A series of sputum tests showed *Candida albicans* and from time to time other species of fungus. A complement fixation test with an antigen prepared from a fungus proved negative. She was treated with potassium iodine which may perhaps have done some good, but it had to be discontinued because of side effects.

Tuberculin tests, frequently repeated, even with Mantoux 1 mg. were completely negative in 29 cases. This may be taken to show that our material may perhaps contain a certain number of cases of sarcoidosis in which the tuberculin reaction is more frequently negative than in a corresponding normal material. In one case, in which there were no other signs of sarcoidosis, Kveim's reaction was faintly positive. There was just one case which might be somewhat suspicious:

A woman, aged 45, gave a history of parotitis and iridocyclitis in January 1938. Some months later bilateral hilus opacities and miliary opacities in both lungs. Considerable progress of the disease, with fibrosis extending from both hili, was observed in 1945. Since then other localizations of the disease have never been found, and Kveim's reaction was negative. She died in her home in 1948 of her pulmonary disease, presumably of cor pulmonale.

In only one of our cases was the pulmonary fibrosis combined with any general systemic disease. There was one case which was probably one of periarteritis nodosa:

A carpenter, aged 49, caught a cold in the Christmas of 1938. «Bronchopneumonia» was discovered subsequently. In 1939 parenchyma opacities and some enlargement of the heart were observed. Cough with expectoration of small blobs. Slight fever. Hemoglobin 105 %. Erythrocytes 5.03 millions/cmm. E. S. R. 116 mm. Eosinophils 6 %. An uncharacteristic rash. Difficulty in eating and extensive, flaccid pareses due to polyneuritis. Proteinuria. A radiological examination showed extensive, striped opacities in both lungs. No record of treatment with sulphonamides. He died on August 6., 1949, and a post-mortem examination showed chronic myositis, bronchopneumonia with congestion, and fatty degeneration of the liver, spleen and kidneys.

In the following two cases. «honeycomb lungs» were found:

(1) A housewife, born in 1901, had suffered from increasing dyspnea about 1912-13. Some dry cough and scanty expectoration. Small hemoptyses now and then. A radiological examination in 1945 showed bilateral, finely spotted infiltration. Unfit for work since 1945 and several stays in hospital. In Medical Department B in February 1948, she suffered from considerable dyspnea without any definite cyanosis. Cough and expectoration scanty. Clubbed fingers. Blood pressure 120/85. Some adventitious sounds over both lungs. Vital capacity 1,600. Mantoux positive and Kveim's reaction negative. No tubercle

baeilli, even after gastric lavage. Hemoglobin 97 %. Erythrocytes 5.18 millions/cmm. A radiological examination showed symmetrical, extensive, massive, bilateral pulmonary infiltrations with numerous clarifications of the size of a pea. These changes seemed to be mainly interstitial in localization, with honeycomb structure. She died in the Opland County Hospital of asphyxia with signs of shock. Myofibrosis with the formation of cysts in the lungs was discovered post-mortem. The case is recorded in full by Jens Hoel (14).

(2) An engineer, born in 1921, fell ill suddenly in January 1949 with stitch in the right side of his chest and high fever. Pneumonia was diagnosed and some sulphonamide treatment was given, but he did not recover completely. A relapse a month later again called for sulphonamide treatment. He was admitted to Vestfold County Hospital, and was subsequently treated in the Medical Department B of the Rikshospital on three occasions. Since March 1949 a dry cough with occasional scanty expectoration and increasing dyspnea. Cyanosis and cor pulmonale with liver congestion set in gradually, and hypertrophy of the right ventricle was observed on electrocardiographic examination. Roentgenograms showed increasing fibrosis, presenting a picture identical with that of myomatosis with numerous small cystic clarifications. Normal findings on bronchoscopy. No tumor cells, and repeated tests for tubercle bacilli negative. Mantoux (3 mg) negative. Hemolytic streptococci found repeatedly in the sputum, but a cutaneous reaction to hemolytic streptococci was negative. Cold agglutination negative. Vital capacity falling: — 3,000—1,800 ml. Arterial oxygen saturation: 87—78 %. Circulation time: ether 7 seconds, deeholin 28 seconds. Venous pressure: 21.5 cm. During his stays in hospital he was a febrile execept for a few jumps to 39°. Blood cultures negative. Now and then transitory acrocyanosis of his limbs thought to be due to vascular spasm. Cortisone had no effect, but transitory and moderate subjective improvement followed ACTH. He died in his home August 1951.

Symptomatology.

In 10 cases the disease was discovered accidentally by an radiological examination (screening). The interval between the first appearance of symptoms (as a rule dyspnea on exertion) and diagnosis was:

Symptom-free	10 cases
0— 1 year	19 »
1— 3 years.....	9 »
3— 5 »	5 »
5—10 »	5 »
over 10 »	6 »

The observation period was:

Less than 1 year	21 cases
1— 2 years.....	10 »
2— 3 »	5 »
3— 5 »	9 »
5—10 »	7 »
over 10 »	2 »

An observation period of less than one year may perhaps not be long enough for us to decide whether fibrosis exists, but in these cases we had reasons for believing that the disease had lasted for a longer time.

We have not been able to contact 12 of our patients since their last stay in hospital.

Cough was the most common symptom:

No cough in	1 case.	No expectoration	1 case.
Slight cough in	11	Insignificant expectoration	23
Moderate cough in	14	Moderate expectoration	8
Considerable cough in	22	Profuse expectoration	14

It is natural to suppose that the patients with periodic attacks of profuse expectoration suffered from secondary bronchiectasis. Nine patients had one or several attacks of hemoptysis. In most of these cases also the hemoptysis was due to bronchiectasis.

Dyspnea.

Dyspnea	11 cases
Slight dyspnea on exertion in	13
Incapacity for great exertion in	11
Total invalidism in	19

Two patients were slightly and 12 were very cyanosed. Eight patients showed increased hemoglobin figures, — men with over 120 % of hemoglobin (Haldane), and women with more than 115 %. Clubbed fingers occurred in 13 cases, and the E. S. R. was raised in very many cases, being under 16 mm only in 16 cases.

The invalidism was first and foremost due to the pulmonary insufficiency with a gradually increasing failure of the right ventricle and cor pulmonale. Most of the cases were not subjected to a special radiological examination with reference to the size of the right ventricle. Eight patients presented quite advanced heart failure with edema, congestion and considerable enlargement of the right ventricle and the picture of cor pulmonale in an advanced stage. Pulmonary hypertension would assuredly have been found in most of our cases. Among all our patients there were 17 with partial, and 19 with complete incapacity for work. In other words, two-thirds of our patients were invalids.

Radiological Changes.

The appearance of these changes may vary greatly in both form and extent. The most common were striped and spotty opacities starting from the hilus and presenting confluent areas to some extent. Eight patients presented purely miliary changes reminiscent of miliary tuberculosis. The typical honeycomb structure was observed in 2 cases.

In 9 cases the hilus glands on both sides were swollen in addition to changes in the parenchyma, and in 14 cases there were pleural reactions of different degrees. Half of these patients had no knowledge of a previous illness affecting lungs or pleurae. Areas of calcification were observed in 6 cases. In 13 cases there were radiological signs of bronchiectases which in 5 cases was verified by bronchography, — a method of examination usually omitted because it was found to be of little diagnostic importance.

We have assessed the extent of the radiological changes using 4 grades. Grade 1 means slight parenchyma opacities, and grade 4 the worst cases with most of the lung tissue on both sides showing pathological changes. Thus classified, our material comes to be grouped thus:

Grade 1.....	10 cases
" 2.....	16 "
" 3.....	26 "
" 4.....	2 "

The clinical manifestations show a certain conformity with the extent of the radiological changes, but in many cases there is a surprising lack of correlation between the two. Two patients included in grade 3 presented no or only quite insignificant subjective symptoms and lacked other objective findings. There was one patient of the miliary type who was discovered by chance by radiological screening. Four patients with extensive radiological changes (grade 3) were perfectly fit for heavy work, one of them being a farmer. On the other hand, many patients suffering from considerable dyspnea on exertion presented slight radiological findings. Among the 10 patients belonging to grade 1 there were as many as 5 who were completely or partially unfit for work. One of them died at home with symptoms indicative of *cor pulmonale*. In conformity with other observers we must therefore insist that the decisive factors are the emphysema and vascular changes about whose importance it is not easy to form an estimate on the radiological evidence.

The extent of the disease likewise did not clearly depend on duration of the symptoms, and in every grade there was approximately the same number of patients with a short or long record of illness. The tendency of the disease to progress must therefore vary very greatly. The same striking discrepancy is to be found when the functional efficiency of the lungs is assessed by their vital capacity. In 4 cases the vital capacity was 1,000 ml or less, two of the patients belonging to grade 2, and two to grade 3. The two patients in grade 4 had a vital capacity between 1,000 ml and 1,500 ml. Among 15 patients (grade 3 and grade 4) there were 10 with a vital capacity under 1,500 ml, and there were none with a vital capacity over 3,000 ml.

Electrocardiographic Changes.

2	electrocardiograms showed	right bundle-branch block.
5	"	" hypertrophy of the right ventricle.
3	"	" flattened T-waves.
2	"	" prolonged P.-Q conduction time.
59	"	" normal conditions.

Among the 59 patients with normal electrocardiograms there were 4 with right axis deviation, 8 with left axis deviation, and 3 with sinus tachycardia. Only one electrocardiogram showed the so-called P-pulmonale with pointed P-wave in the II. and III. lead. None showed P-mitrale. It is generally agreed that these auricular changes revealed in an electrocardiogram are very rare. Changes in the ventricular complex are also rare as shown by our material.

Clinical Course.

Prolonged observation is necessary to decide whether the disease is stationary or progressive, and also to gauge its influence on the lungs and circulation. All of the patients have been written to and requested to send a new radiogram, and some have been readmitted to hospital for re-examination. We have been unable to trace 12 patients. When patients have died away from hospital, we have obtained information about them from their relations or doctor. Altogether 20 of our patients died, one from some unknown cause and one from some intercurrent disease. Neither of the last two presented subjective lung symptoms. All the other 18 patients died with signs of progressive cardiac and pulmonary insufficiency, but without, as a rule, progressive radiological changes. In all probability the cause of death in these cases was chronic cor pulmonale.

At the time of death the patients' ages were:

Between 30 and 40 years in 1 case.				
•	40	•	50	• • 6 cases.
•	50	•	60	• • 7 •
•	60	•	70	• • 6 •

None of the 23 patients with the diagnosis of Boeck's sarcoid had died by the beginning of 1951.

The interval between the onset of symptoms and death was:

Less than 1 year in 1 case				
	1	to	2 years	• 2 cases
3	•	4	•	• 4 •
4	•	6	•	• 2 •
6	•	10	•	• 2 •
Over	10	•	•	7 •

In some cases there was a history of illness for more than 20 years, but with rapid deterioration during the last two years preceding death.

It is difficult on the clinical evidence to decide which factors dominate the prognosis. Once signs of cor pulmonale have appeared the prognosis is bad. Among the 18 who died of cor pulmonale there were 14 with radiological changes corresponding to grades 3 and 4. Four patients showed less extensive changes which in one case corresponded to grade 1. This patient suffered from emphysema, bilateral involvement of the pleurae, and typical cor pulmonale on admission to hospital. We may assume that the emphysema and vascular changes were the main factors responsible for pulmonary hypertension, and these changes are not radiologically demonstrable when the parenchyma is involved.

A post-mortem examination was carried out in 6 cases. Myomatosis (14) was found in one case. Fibrous changes and broncho-pneumonic lesions in the lungs, to some extent with bronchiectasis, were found in the other cases. In 2 cases amyloid disease and fatty degeneration of the liver, kidneys and spleen were found. The course of the disease in the 34 survivors was, as judged by the radiological findings, as follows:

Progress of the disease	in 3 cases
No change	" 18 "
Regression of the disease	" 3 "
No observation	" 10 "

Among the 3 patients showing regression of the disease there were 2 in which this may perhaps have been in doubt as the chest X-rays were not altogether comparable. On the whole, the pulmonary fibrosis which has reached the stage of being radiologically demonstrable is a stationary process. The clinical signs of progress of the disease depend on the secondary vascular changes and the increase of emphysema. One patient showed remarkable improvement, although the roentgenogram taken on the first occasion suggested that the fibrous changes were irreversible.

Subjective improvement was experienced by 2 patients without any radiological evidence of regression of the disease. Four patients showed considerable clinical deterioration without radiologically demonstrable progress of the disease. Of course the pulmonary hypertension can by itself lead to increasing failure of the right heart even when the pulmonary changes are stationary. The emphysema clearly may also be progressive. Thus, several of the patients who died showed no change in the radiological picture for several years before death occurred.

Treatment.

We do not propose to discuss treatment in detail, but would like to point out that ACTH and cortisone have also been tried in the present material, sometimes in quite large doses, but without any demonstrable effect. The recession of the disease reported from several quarters after treatment of this disease with ACTH and cortisone may be due to the pulmonary changes having been provoked only to a slight degree by irreversible fibrosis.

Summary.

From a medical department, 54 cases of bilateral pulmonary fibrosis of unknown origin have been collected in the course of 10 years. To these cases 23 are added in which Boeck's sarcoid was diagnosed. The etiology and pathogenesis of pulmonary fibrosis are surveyed, and attention is drawn to certain characteristic and less well-known forms of disease. The radiological changes may vary very greatly and can give no clue to the etiology. It is also impossible radiologically to distinguish between Boeck's sarcoid and the other forms of chronic, bilateral pulmonary infiltration. In about 15 % of the cases, the first symptoms appear as a sequel to acute infections of the lungs, and in the history of one-third of these cases there is a record of a previous attack of pneumonia or pleurisy which usually, however, dates back several years before the first appearance of clinical symptoms. In two-thirds of these cases the disease begins insidiously, lasting for a long time without symptoms. In many cases the diagnosis is made by chance as the result of a routine radiological screening.

In addition to opacities of the parenchyma, changes in the pleurae are to be found in fully a quarter of these cases, and signs of bronchiectasis are demonstrable

also in about one-quarter. Six of our patients showed opacities due to calcification, and 2 of them showed a radiologically demonstrable honeycomb structure with numerous cystic clarifications which are characteristic of myomatosis.

In many cases the symptoms bear no relationship to the extent of the radiologically demonstrable changes, and progress of the disease varies very greatly. Sooner or later, signs of cor pulmonale appear in most cases. Among our patients there were 19 quite unfit for work and 17 partially so. Among the 43 patients followed up there were 18 who died of cor pulmonale. In about half of these cases death occurred within 5 years of the appearance of the first symptoms. The clinical symptoms may progress even when the radiological findings are stationary. The prognosis is determined by the development of the emphysema and the vascular changes. Six of our patients underwent a post-mortem examination, and in one of them diffuse myomatosis with cystic changes was found.

References.

1. Baldevin, E. F., Courmand, A. & Richards, D. W. jr.: *Medicine* 1948: 27: 243. —
2. Church, R. E. & Ellis, A. R. F.: *The Lancet* 1950: 258: 392. — 3. Coope, R.: *Diseases of the chest*. Edinburgh 1945. — 4. Dreyer, V.: *Nord. Med.* 1951: 45: 734. — 5. Edmunds, Ph.: *Brit. Med. J.* 1946: I: 127. — 6. Felson, B., Jones, G. F. & Ulrich, R. P.: *Am. J. Roentgenol.* 1950: 64: 740. — 7. Friend, J. & Thackray, A. C.: *The Lancet* 1950: 2: 909. — 8. Galdston, M., Weisenfeld, S., Benjamin, B. & Rosenbluth, M. R.: *Am. J. Med.* 1951: 10: 166. — 9. Gouley, A. B.: a) *The Am. J. Med. sc.* 1938: II: 1. b) *The Am. J. Med. sc.* 1938: II: 0. — 10. Gray, F. D. jr., Lurie, P. R. & Wittemore, R.: *Yale J. Biol. & Med.* 1951: 23: 380. — 11. Hamman, L. & Rich, A. R.: *Bull. of the Johns Hopkins Hospital* 1944: I: 177. — 12. Hodgson, C. H., Weed, L. A. & Clagett, O. T.: *J. A. M. A.* 1951: 145: 807. — 13. Hoel, J.: *Nord. Med.* 1949: 42: 1273. — 14. Liavaag, K.: *Nord. Med.* 1949: 30: 1276. — 15. Licht, E. de Fine: *Acta Radiologica* 1942: 23: 151. — 16. Lindskog, G. E.: *Yale J. Biol. & Med.* 1951: 23: 311. — 17. Mallory, T. B.: *Radiology* Syracuse, N. Y. 1948: 51: 468. — 18. Muirhead, E. E. & Haley, A. E.: *Arch. Int. Med.* 1947: 80: 328. — 19. Nelson, C. T.: *Arch. Dermatology and Syphilology* 1949: 60: 277. — 20. Olsen, H.: *U. F. L.* 1950: 112: 758. — 21. Oswald, N. & Parkinson, Th.: *Quart. J. Med.* 1949: 18: 1. — 22. Parkinson, Th.: *Brit. M. J.* 1949: I: 1029. — 23. Penbody, H. D. jr., Morecha, H. J. & Edwards, J. E.: *J. Thoracic Surg.* 1951: 21: 519. — 24. Potter, B. P. & Gerber, I. E.: *Arch. of int. med.* 1948: II: 113. — 25. Rasmussen, H. & Storstein, O.: *Acta Med. Scand.* 1951: 141: 43. — 26. Reiersol, S.: *Tidskr. f. Den Norske Lægeforening* 1952: 13—14: 434. — 27. Robbins, L. L. & Sniffen, R. C.: *Radiology* 1949: 53: 187. — 28. Roendal, Th.: *Acta Radiologica* 1942: 23: 138. — 29. Samuelsen, E.: *Acta Radiologica* 1942: 23: 575. — 30. Seldin, D. W., Kaplan, H. S. & Bunting, H.: *Ann. Int. Med.* 1947: 26: 196. — 31. Sjøberg, S.-G.: *Nord. Med.* 1950: 43: 117. — 32. Spain, D. M.: *Ann. Int. Med.* 1950: 33: 1150. — 33. Spain, D. M. & Thomas, A. G.: *Ann. Int. Med.* 1950: 32: 152. — 34. Storstein, O.: The effect of pure oxygen breathing on the circulation in anoxemia. A S John Griegs Boktrykkeri, Bergen 1952. — 35. Storstein, O.: *Tidskr. f. Den Norske Lægeforening* 1952: 13—14: 426. — 36. Sundgaard, G., Thjøtta, Th. & Urdal, K.: *Nord. Med.* 1950: 1: 434. — 37. Sundin, T. og Tomenius, J.: *Nord. Med.* 1950: 1: 781. — 38. Taquini, A. C., Fasciolo, J. C., Suarez, J. R. E. & Chiodi, H.: *Arch. Int. Med.* 1948: 72: 531. — 39. v. Stoessel: *Beitr. z. Klinik d. Tuberkulose* 1937: 90: 422. — 40. Waddell, W. R., Sniffen, R. C. & Sweet, R. H.: *J. Thoracic Surg.* 1949: 18: 707. — 41. Wilson, R. H., Borden, C. W. & Ebert, R. V.: *Arch. Int. Med.* 1951: 88: 581. — 42. Winn, W. A.: *Arch. Int. Med.* 1951: 87: 514. — 43. Wright, G. W. & Filley, G. F.: *Am. J. Med.* 1951: 10: 642.

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Acute Non-Specific Pericarditis.

Study in 24 Cases Including Descriptions of 2 with Later Development into Constrictive Pericarditis.

By

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Since the publication of Barnes and Burchell's paper in 1942 acute non-specific pericarditis (a. n. p.) has received increasing attention as a syndrome *per se*, and several compilations of the entity have been presented by such authors as Nathan and Dathe (1946), Nay and Boyer (1946), Logue and Wendkos (1948), Evans (1950), Levy and Pattersson (1950), Parker and Cooper (1951) and Carmichael et al. (1951). Most of these investigators stress the benign character of the disease and the difficulty in distinguishing the condition from myocardial infarction.

Only a fairly few cases have been described in Scandinavia. Engelfeldt (1952) in Sweden reported 5 cases. A number of cases have been published in Denmark by Bing (1933), Heckscher (1933), Thune Andersen (1948), Aagaard and Jensen (1952), Gormsen (1952); most of these cases appeared in association with epidemic myalgia. However, the 4 cases described by Andersen (1948) were probably of another origin and were classed by him under the heading *pericarditis sicca juvenilis benigna*. It is questionable whether the cases of genuine, acute pericarditis described in American literature are of the same or related origin as the cases described in Denmark.

The increasing frequency with which a. n. p. has been recognized during the last decade may be due to a true increase in the incidence of the condition. On the other hand it may be only apparent and explainable by the increased attention given to the syndrome as a clinical entity and its classification as such instead of pericarditis secondary to rheumatic fever, for example, or as myocardial infarction. As pointed out above, the clinical picture of acute pericarditis closely resembles that of myocardial infarction, a similarity that has probably not always received adequate attention.

With this in mind it was thought justified to check a series of cases diagnosed as myocardial infarction, especially cases seen in patients below 45 years of age, when a. n. p. is most common.

In order to get an idea of the frequency of a. n. p. in relation to other types of pericarditis the records of all cases of pericarditis and those cases of myocardial infarction diagnosed in patients under 45 years of age (54) and seen at Malmö general hospital during a 10-year period (1943—1952) were analysed. Analysis of the myocardial infarction series revealed that in 3 of the patients, aged 21, 30 and 42, the disease should have been classed as a. n. p., and that in another case in a patient aged 25 the observations also suggested a. n. p. as the most probable diagnosis.

The receiving area of Malmö general hospital has a population of about 200,000 inhabitants, all of whom are catered for by this hospital only. The present series, which includes all cases of pericarditis in patients above 15 years seen at the department of medicine, the department of tuberculosis and the department of infectious diseases, may thus be taken as representative of inhabitants above 15 years in this receiving area and at the same time provide a fairly reliable measure of the frequency of the different types of pericarditis per 200,000 inhabitants.

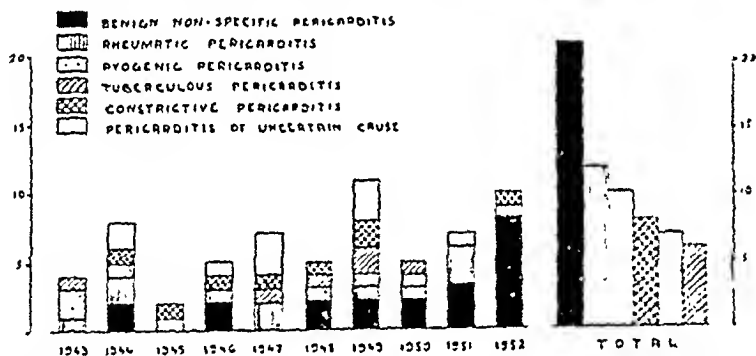


Fig. 1. Frequency of various types of pericarditis seen at Malmö general hospital during the 10 year period 1943—1952 in patients above 15 years of age.

The annual and total frequencies of the various types of pericarditis are apparent from Fig. 1. The series includes all cases of pericarditis except those seen in association with uraemia, myocardial infarction and tumours involving the heart. Of these 64 cases of pericarditis, 21 were diagnosed as a. n. p., 8 as constrictive, 12 as rheumatic (in 2 of these the condition might have been due to Lupus erythematosus disseminatus), 7 as secondary to acute bacterial infections of the thorax, 6 as tuberculous and 10 of unclassifiable type. As is apparent from the figure a. n. p., which occurred only sporadically in the beginning of the 10-year period, hardly 2 per year, was much more common in 1952, when it was seen in as many as 8 patients — an increase that can hardly be ascribed to chance.

In the present series a. n. p. was by far the most common type of pericarditis and even much more common than rheumatic pericarditis, which had hitherto

been regarded as the predominant type. This shift in rank must, however, be seen in the light of the fall in the frequency of rheumatic fever during the last few years.

Only few statistical analyses of the frequency of the various types of acute pericarditis in a representative population are on record. Recently Reeves (1953) published a report on 96 cases of acute pericarditis diagnosed during a 16-year period (1935—1950) at a general hospital in New York. He studied the cases with special regard to the causative agents and it was noted that rheumatic fever accounted for 40.6 %, purulent pericarditis for 19.7 %, tuberculous pericarditis 7.3 %, benign, non-specific pericarditis 10.4 %, uraemia 11.5 %, neoplasm 2.1 % of the 96 cases.

As the true etiology of a. n. p. is not known, it has also been called acute idiopathic pericarditis. Judging by the variability of the clinical course from one case to another, the disease can probably be caused by more than one agent: therefore the term acute, non-specific pericarditis must for the time being serve as a collective name for those cases of acute pericarditis in which no systemic or local causal agent can be demonstrated.

The most characteristic symptoms forming the basis of the diagnosis were as follows.

The onset, which is usually preceded or accompanied by symptoms of some slight infection of the upper respiratory tract, is characterized by the occurrence of more or less severe substernal or precordial and often radiating pain, which is accentuated by deep respiration, cough or motion, sometimes even by swallowing. Common observations in the early stage of the condition are: widespread pericardial friction rub, fever, leukocytosis and typical electrocardiographic abnormalities such as initial elevation of the S—T segments followed by depression or inversion of the T waves in 2 or more leads. Co-existent pneumonia and/or pleurisy is not uncommon, and chest x-ray examination often reveals transient enlargement of the heart shadow as a sign of pericardial exudate and/or dilatation. The condition usually passes off fairly soon, but it has a tendency to recur.

Clinical observations made in 24 cases of acute non specific pericarditis are summarised in table 1.

Age and sex. The ages of the patients ranged from 16 to 64 years (average 37 years). These figures agree approximately with those in series published by other workers in this field. Only 3 of the cases were seen in females. In Barnes and Burchell's series the average age was 42, in Levy and Patterson's it was 35 (12—43), in Nay and Boyer's it was 27 (20—37) and in Parker and Cooper's it was 33 (19—45). In all of these series males were likewise preponderant.

Chest pain. Chest pain, usually substernal or precordial, is the dominating symptom and careful investigation of nature of this pain is of great differential-diagnostic importance. The site and radiation of the pain is on the whole the same as in myocardial infarction. Thus pain radiating to the left shoulder was noted in 3 of the cases, to the left arm in 3, to both shoulders in 3, to both arms in 3, to the right shoulder in 3, to the right arm in 1: in 3 of the cases the pain also radiated to the throat and neck and in 2 to the back. The onset of pain is often sudden,

Table 1.

Symptoms and Signs in 24 Cases of Non-Specific Pericarditis

1. Chest pain (substernal, precordial, left thorax)	25	100 %
Radiation of pain (to one or both shoulders and arms, neck and back)	17	
Pain intensified on movement, breathing or coughing	23	
Recurrent pain	11	
2. Ekg-changes	23	95 %
S—T elevation (1 in 1 lead, 5 in 2 leads and 12 in 3 or more leads)	18	
T wave inversion (2 in 1 lead, 6 in 2 leads, 10 in 3 or more leads)	18	
T wave lowering without inversion	2	
P—Q prolongation	1	
3. Fever	21	87 %
4. Increased sedimentation rate (> 15 mm/h hour)	21	87 %
5. Pericardial friction rub	17	70 %
6. Preceding upper respiratory infection	13	54 %
7. Heart enlargement	11	45 %
8. Pleuritis (effusion)	11	45 %
9. Cough	10	41 %
10. Dyspnoea	10	41 %
11. Leukocytosis (> 10,000)	8	33 %
12. Pneumonitis	5	20 %
13. Initial abdominal pain	5	20 %
14. Headache	2	
15. Jaundice	1	

and although the pain is usually not so severe as in myocardial infarction, it is sometimes accompanied by symptoms of circulatory collapse. Symptoms of circulatory disturbances were also seen in a few of our cases. The pain is not of the 'gripping' type described in myocardial infarction, nor is it accompanied by a state of anxiety. Of diagnostic importance is whether the pain is accentuated by deep respiration, cough and motion, these symptoms being rare in patients with pericarditis secondary to myocardial infarction. In patients with a. n. p., this accentuation of the pain on deep respiration, cough or motion usually appears very soon after the onset of the disease, while in myocardial infarction it does not make its appearance until a few days after the onset.

Abdominal pain was reported as the initial symptom by 5 of the patients. In 3 of them the pain was localised to the epigastrium. As to the other 2 patients, in one of them the onset was accompanied by acute pain in the lower part of the abdomen: appendicitis was assumed and he was admitted to the department of surgery for observation. After a day or so abdominal pain subsided, but now the patient complained of precordial pain, and pericardial friction rub was audible. In the other patient the onset was accompanied by severe abdominal pain, vomiting and diarrhoea and within a few hours typical precordial pain appeared. The possibility of co-existent peritoneal serositis as a local manifestation of more or less generalised serositis cannot be excluded. Pleural affection in association with acute pericarditis is not uncommon either.

* Three of these cases were seen in 1953 and are therefore not included in the 10-year series.

A symptom-free interval of a few days to a few weeks is not rarely followed by an exacerbation of the pain, frequently accompanied by fever and sometimes with the return of the precordial friction rub. This was observed, for example, in case 22, in which 3 such exacerbations were noted. In our series 8 of the patients experienced recurrences of the pain within the first month of the onset usually after a remission of a week or so. In 5 of them the exacerbation was accompanied by fever. Parker and Cooper reported such recurrences in half of their 22 cases.

That the disease is also capable of recurring after an interval of months or even years, has been observed by many workers in this field, especially by Tomlin, Logue and Hurst (1952), who described 8 cases of the disease in which the number of recurrences ranged from 2 to 19. In 1 of their cases the patient was a woman, aged 27, who had since the age of 8 had altogether 19 seizures of sudden, severe substernal or precordial pain accentuated by deep respiration. The longest remission was 4 years. Levy and Pattersson (1950) described 4 recurrences in 3 patients, in 2 of them 8 and 10 years respectively after the initial onset. Recurrent chest pain was also noted in 5 of the present cases: in 1 of them chest pain, electrocardiographic changes and co-existent pleurisy were noted 4 months after the initial seizure, 1 had recurrent substernal pain 6 months after the onset, 1 patient reported that he had once chest pain 1 year before the seizure for which he was admitted to hospital and 1 had a recurrence 14 months after the onset (he had in the meantime had aseptic benign meningitis, possibly due to the Coxsackie virus). The fifth patient had had 8 attacks during the last 10 years, usually with fever; it appears, however, that pericarditis was not recognized until the last attack in 1952. On earlier occasions the patient had been treated at various military hospitals during World War II.

In none of the patients who had experienced recurrences could any signs of persistent myocardial or pericardial damage be demonstrated.

Case 22. The patient, a male aged 16, was admitted to hospital on Nov. 16, 1952, two days after the onset of pain under the left arcus costarum in association with deep respiration or coughing. He reported that he had had a chill, cold in the head and cough for about a month. In the beginning the pain was only moderate and he went to school as usual on the Nov. 15th, *i. e.* the day before admission. He did not measure his temperature that day. The following day he suddenly felt much worse: deep respiration or cough was accompanied by severe pain retrosternally and to the left of the sternum and subsequent shortness of breath. He found it painful to lie flat; forward bending in the sitting posture gave slight relief. He had a slightly productive cough.

On admission on Nov. 16. When he lay on his back he had severe dyspnoea, which subsided when he sat up. He appeared slightly anxious. Temp. 38.7 C. The pharyngeal mucosa was slightly reddened. Auscultation: distinct, somewhat dull heart sounds without friction rub. Heart beat: about 110/min. Blood pressure: 110/70 mm Hg. The abdomen felt soft and was not tender. The liver and the spleen were not palpable.

X-ray examination. On Nov. 16th revealed slight mottling of the base of the left lung and slight enlargement of the heart. Electrocardiographic studies that day showed elevation of the ST segment in leads I, II and IV. The following day the patient felt worse: he was now really ill and listless and had in addition become icteric. The heart sounds were weaker, the serum bilirubin was 2.5 mg/100 ml. White count 15,500. There were no signs of venous stasis. Temp. 38.5 — 39 C. By the 19th, *i. e.* 2 days later the con-

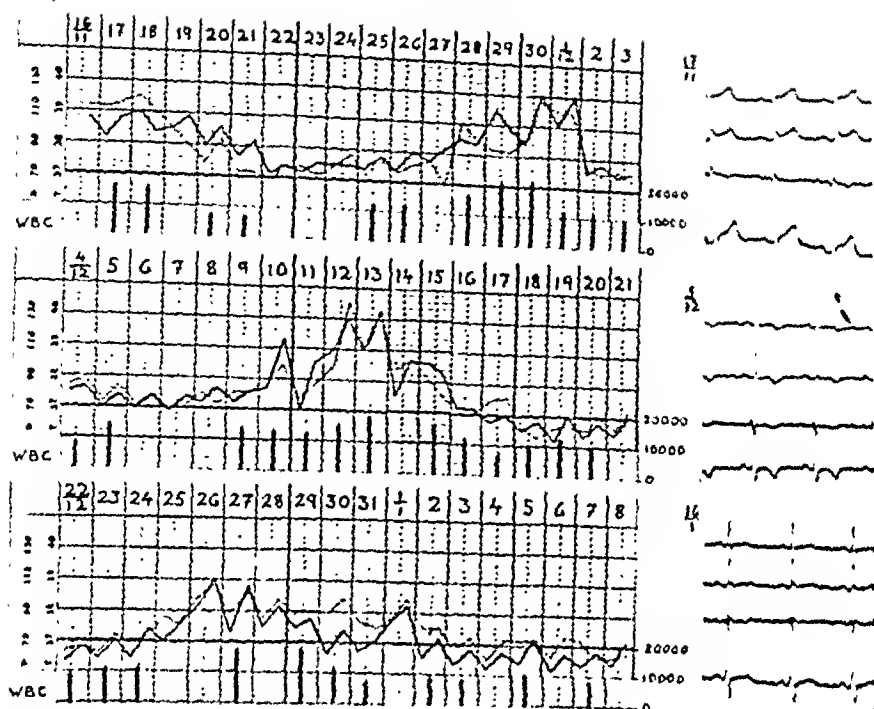


Fig. 2. Temperature chart, W. B. C. and electrocardiograms in a case of acute benign non-specific pericarditis (G. W., 16 years, case 22) with recurrent attacks of fever and chest pain.

dition began to clear up: the pain had practically disappeared, the interns had subsided, now, for the first time, distinct precordial friction rub was heard: this rub increased in intensity, and during the next few days it was heard over the entire precordium. On 20th Nov. the patient began to receive aureomycin, and X-ray examination that day revealed considerable enlargement of the heart, the left border of which now almost reached the lateral wall of the thorax. A small filling was now also seen in the left sinus. The venous pressure was 13 cm; the temperature had begun to return to normal and the patient felt well. On Nov. 24th X-ray examination showed that the enlargement of the heart had subsided (vol. 600 cub. cm/square metre body surface). In the base of the left lung, however, faint mottling of the parenchyma persisted. On Nov. 25 electrocardiographic studies showed inversion of the T waves in all leads (I, II, III, IV and V₆). A new bout of fever with peaks of 40° C during aureomycin therapy was accompanied by precordial pain radiating to the left shoulder and a return of the pericardial friction rub. This rub, which had been absent for 2 days, now persisted for a few days. The white count was now 21,000, and the X-ray film again showed enlargement of the heart (vol. 650 cub. cm/square metre body surface). This enlargement persisted until Dec. 5 i.e. after the patient had been afebrile for 5 days. However, signs of parenchymal change in the base of the left lung and slight pleural effusion were still seen. On Dec. 12 the patient experienced a third bout of fever, which lasted for a week, during which peaks of 40° C were recorded. During that week he sometimes had chills and occasionally he had slight precordial pain when he turned in his bed or when he breathed deep. This pain radiated out into both shoulders. During a day or so weak precordial friction rub was also felt. X-ray examination on Dec. 19 showed further decrease in the size of the heart (520

cc/sq. metre body surface) and regression of the basal parenchymal changes. The electrocardiogram still showed negativity of all T waves. From Dec. 25 to Dec. 29 the temperature was again elevated (39° C) and the white count was increased (17,600), but during this time the patient felt well, he had no pain and no precordial friction rub was audible. The patient was sent home on Jan. 20, 1953, after 3 weeks' afreibility and absence of symptoms, and after X-ray examination on Jan. 16 had shown that the enlargement of the heart still demonstrable in the X-ray film taken at the end of December 1952 had completely subsided (415 cub. cm/sq. metre body surface). The electrocardiogram traced on Jan. 17 showed no changes: all T waves were positive.

Other laboratory findings. The sedimentation rate, which was 10 mm on admission, increased to 68 mm/hour on Nov. 20, after which it fluctuated between 30 mm/hr. and 40 mm/hr. until Dec. 27, when it increased to 55 mm/hr. after which it gradually returned to normal. The fluctuation in the white count is apparent from Fig. 2. The venous pressures recorded were: 13 cm (Nov. 21); 21 cm (Dec. 5); 11 cm (Dec. 10); 10.5 cm (Jan. 15).

Cold agglutination tests on Nov. 17, Nov. 28 and Dec. were negative. Widal reaction on Dec. 31 was negative. Culture of blood drawn on Nov. 17, Dec. 11 and Dec. 12 gave no growth. The tuberculin reaction (Mantoux 1 mg) was negative. Studies for the presence of C-virus were negative.

The electrocardiographic changes seen in pericarditis are characteristic and almost invariably present and therefore of great diagnostic value. These changes are due to a): the pericarditis *per se* b): the extent of injury to subepicardium and possibly to deeper layers of the myocardium and to c): the amount of pericardial effusion. It is the subepicardial myocarditis that is believed to be the main cause of the electrocardiographic abnormalities: but it is not possible to draw a sharp line of distinction between the more or less specific pattern of pericarditis and that of myocarditis.

The electrocardiographic changes seen in acute pericarditis have been described in detail by Bellet and Mc Millan (1938), Vander Veer and Norris (1937 and 1939) and by Noth and Barnes (1940).

The elevation of the S—T segment, often with upwards concavity, is the most characteristic change in the early stage of the disease. This change is usually seen in all leads, but may occur in leads I and II or II and III or, though rarely, in lead I only, with or without elevation of the S—T segments in the precordial leads. The S—T changes are sometimes very transient, as in one of the present cases, in which they disappeared within a day, though they usually persist for a few days to a week. Carmichael et al. (1952) observed no elevation of S—T segments after 12 days in their series. In 3 of the present cases S—T elevation persisted for 3—5 weeks, but in 2 of them no changes in the T waves were seen. The elevation of the S—T segments in pericarditis differs from that seen in myocardial infarction by its usual appearance in more than 2 of the standard leads, by the usual but not invariable presence of its upward concavity, but above all by the absence of reciprocal depression of the S—T segments in other leads (I or II) usually seen in myocardial infarction. In pericarditis the S—T-changes always occur in the same direction, although Barnes and Burchell (1942) have described 1 case with reciprocal changes.

The T waves may be abnormally high in the initial stage of the disease, but

after about a week they begin to decrease or, what is more usual, become inverted and may remain so for several days to several months. This inversion is usually seen in two or more leads, though in rare cases it may appear in one only. Occasionally only small changes of the T waves are recorded, and in some cases the abnormal T waves are the only electrocardiographic changes seen, which is probably explained by the frequently very transient nature of the S—T elevation or by the varying interval between the onset of the disease and the initial examination. During recurrences the changes of the S—T segments and of the T waves sometimes fluctuate.

Inversion of the T waves seldom occurs until the S—T segments have returned to the iso-electric level, an observation which, according to Nay and Boyer (1946), is of value in distinguishing pericarditis from myocardial infarction.

The Q waves. In contrast to myocardial infarction and in accordance with reports by other workers in this field, the Q waves showed no characteristic changes in the present series.

The QRS complex in pericarditis is usually normal. However, in the presence of pericardial effusion the voltage is sometimes low. Barnes and Burchell (1942) described such diminished voltage in a case in which the pericarditis was of more chronic or subacute type. QRS deformation otherwise suggests more severe myocardial injury and argues against a. n. p.

Prolongation of P—Q interval does not occur in a. n. p., but is common in rheumatic pericarditis. However, transient prolongation of the P—Q interval to 0.24 was recorded in one of the present cases in which the clinical picture included nothing suggestive of rheumatic fever. The patient was a man, aged 46, with histologically verified (liver biopsy) haemochromatosis but with only slight clinical manifestations. Acute, non-specific pericarditis in association with haemochromatosis has been described before (Pohl 1950 and Godfrey 1951) and it is possible that the pericarditis and the prolonged conduction time were due to a deposition of haemosiderin in the pericardium and myocardium.

Cardiac arrhythmias were not observed in any of the present cases, but Levy and Pattersson (1950) described 3 cases with auricular fibrillation, Parker and Cooper (1951) 1 case with paroxysmal auricular flutter, Gilley et al. (1951) 2 cases of paroxysmal supraventricular tachycardia, which has also been reported by Wolff (1943).

According to most reports, the electrocardiographic changes disappear some 6 to 8 weeks after the acute phase. This fairly early disappearance of electrocardiographic abnormalities is one of the most important features distinguishing pericarditis from myocardial infarction. In rare cases, however, the normal T waves may persist for months or even years (Gilley et al. 1951, Carmichael et al. 1951, Godfrey 1951, Pohl 1951). Of those cases of the present series that were regularly followed electrocardiographically, the pattern had recovered its normal appearance within 8 weeks in all except 2. In one of these 2 the changes were still persistent when the patient was last seen one year after the attack and in the other (Case 14 described below) in which constrictive pericarditis developed, the electrocardiographic pattern was abnormal for at least 6 months.

Although electrocardiographic changes appear to have been regular findings in most series on record, cases of clear-cut pericarditis without associated electrocardiographic abnormalities have been seen. Levy and Pattersson (1950) found 1 such case in their series of 27 patients; Evans (1950) 1 of his 11 cases and Bellet and Mc Millan (1938) found no such changes in 12 of 57 cases of acute pericarditis, 7 of which were of unknown origin.

In the present series no electrocardiographic changes were seen in 1 case of pericarditis in which the clinical symptoms were not prominent either. This case and case 22 described above may be regarded as extremes of the long scale of variation of the clinical course of a. n. p.

Case 13. The patient was a woman, aged 24, who was first seen at Malmö general hospital on Dec. 12, 1951. She reported that she had 2 days earlier experienced pain in the left half of the chest. The pain, which radiated to the left shoulder, then also to the back, was accompanied by weakness of the left arm. The symptoms had subsided towards evening but returned the following evening. She herself had felt and heard a grating sound in the region of the heart: the sound was synchronous with the heart beat, but not with respiration. The patient consulted her doctor, who recognised pericardial friction rub, a finding now confirmed at examination on admission of the patient to hospital. It was heard at the level of the fourth rib to the left of the sternum. The friction rub passed off within 12 hours and the patient was then symptom-free. Apart from this rub, physical examination revealed no signs of disease; there was no dyspnoea, no cough, the temperature was normal, the white count was 4,200, S. R. 9 mm/hr., the ECG-pattern was normal and chest X-ray showed no enlargement of the heart or lung changes. The antistreptolysin titre was normal.

Pericardial friction rub. Auscultation must often decide the diagnosis: therefore in the absence of such rub the examination should be repeated fairly often. In less typical cases the rub is inconstant, it may only be heard now and then and disappear altogether after a day or so, but it may persist for weeks. The frequency with which this rub is heard in a given series therefore varies with the thoroughness with which it has been sought. Judging the literature it is audible in about 75 per cent of all cases. In the present series friction rub was noted in 70 per cent with an average duration of 5 days (range 1—21 days). In 1 of the cases with eight recurrences within 10 years, the rub persisted for 21 days. Carmichael et al. (1951) reported an average duration of 9 days for their series (50 cases), in which the rub persisted for 60 days in 1 of the patients.

Friction rub is also heard in some 10 to 20 per cent or more of all patients with myocardial infarction. Certain differences between the friction rub of pericarditis and the friction heard in myocardial infarction are of differential diagnostic value. In a. n. p. the friction usually appears soon after the onset of the disease, often already on the first day: in myocardial infarction they are not heard until the second or third day. The friction is also usually louder and often more constant and is heard over a larger area than in myocardial infarction, in which the rub is less persistent and frequently localised to a smaller area.

Fever. More or less pronounced fever is a practically regular initial symptom and was recorded in 21 out of the present 24 cases: in 12 of them peaks of 39° C or more were registered and in 5 chill were also noted. The fever persisted for 3 to 21

days (average 11 days). The shape of the temperature curve is surely often informative in the distinction of the disease from myocardial infarction, in which the temperature curve usually shows a very characteristic shape: the temperature does not reach a maximum until the second or third day, seldom over 39°C , and then returns typically to normal within 10 days in uncomplicated cases. A temperature of this regular appearance is not typical of acute, non-specific pericarditis, in which recurrent bouts of fever are not uncommon.

Leukocytosis (more than 10,000 white blood cells per cubic millimetre). Leukocytosis has been described as common in pericarditis (Cooper et al. 65 per cent; Levy and Patterson 80 per cent), but in the present series it was noted in only about one third of the cases.

Increased sedimentation rate (> 15 mm/hr.). The sedimentation rate is usually, though not invariably, increased. It was noted in all of the present cases except 3. The highest values measured varied from 15 to 102 mm/hr. and the average was at most 48 mm/hr.

X-ray examination. Roentgenographic examination showed enlargement of the heart shadow in 11 of the 22 patients examined. In several cases, however, the examination was not performed as long as the disease was in the acute stage, probably because of the difficulty in excluding myocardial infarction. The heart was enlarged in 9 of 12 patients examined roentgenographically within 10 days of the onset.

Transient enlargement of the heart shadow in the acute stage is common. Ordinary roentgen examination will usually not permit a decision as to whether this enlargement is due to dilatation of the heart or to pericardial effusion. Levy and Patterson (1950) who found an enlargement of the heart shadow in 20 of 25 cases interpreted it as dilatation in 15 of them. Carmichael et al. (1950), who found such enlargement in 25 of their 50 cases, attributed it to pericardial effusion in 3 and to dilatation in the remainder. Other workers in this field believe pericardial effusion to be the commonest cause of enlargement of the heart shadow. It is probable that the only way to decide the origin of such enlargement is to puncture the pericardium: this was done by Nathan and Dathie (1916) who found the punctate to be haemorrhagic in 4 out of their 8 cases. Porter et al. (1950) found a sanguinous effusion in all of their 4 cases. Mc Cord and Taguchi (1951) described 1 case with a fatal issue which, according to them was due to the fact that treatment with anticoagulants because of assumed myocardial infarction had increased the bleeding in the pericardium and caused cardiac tamponade. In the light of this observation they warn against the use of anti-coagulants in the management of acute, non-specific pericarditis.

It can hardly be advisable to perform pericardiocentesis in a. n. p. unless the clinical picture includes definite symptoms of cardiac tamponade, which have, however, otherwise never been reported in series available. Parker and Gump (1951) stressed the value of angiocardiology in distinguishing dilatation of the heart from pericardial effusion. They say that unless the patient actually has heart failure, the danger of angiocardiology is not great.

The value of kymography is limited because a flabby, dilatated heart can convey an impression similar to that of pericardial effusion.

Roentgen examination often shows not only enlargement of the heart but also pneumonitis and/or dry or wet pleurisy. Of our 24 cases dry pleurisy was seen in 2 and wet pleurisy in 8. In 7 cases the pleurisy was localised to the left side and in 3 it was bilateral. Only in 5 cases signs of pneumonitis were observed.

Antistreptolysin titre. Of the 20 cases studied the level was normal in 15 and increased (more than 200 U) in 5: 500 U in 2, 425 U in 1, 280 U in 2. In none of these cases was further evidence of rheumatic affection: none of the patients had joint pain and in none was there any change in conduction time or of the QRS complex in the electrocardiogram.

Differential diagnosis. Cardiac infarction, rheumatic fever, tuberculosis and purulent pericarditis as well as non-rheumatic myocarditis must be excluded before a diagnosis of a. n. p. can be established.

Careful investigation will in most cases permit differentiation between acute, non-specific pericarditis and myocardial infarction, even though it may sometimes not be possible to clear up the diagnosis with certainty. Differentiation is of prognostic importance in the evaluation of the future working capacity and from a point of view of insurance. Moreover, a. n. p. is frequently seen in young persons; in these the consequences of an erroneous diagnosis of myocardial infarction are obvious. Differentiation is also of therapeutic importance, it being known that anti-coagulation therapy is contra-indicated in the management of a. n. p.

The following observations may be useful in the differentiation of acute, non-specific pericarditis from myocardial infarction.

1. The onset of a. n. p. is often (60—80 per cent of all cases) preceded by infection of the upper respiratory tract.
2. Pain or increased pain on deep respiration, coughing and on movement are the most regular symptoms in pericarditis.
3. The character of the friction rub is sometimes of differential-diagnostic value: the friction should therefore be regularly followed.
4. Daily electrocardiographic studies during the acute stage facilitate differentiation.
5. The shape of the temperature curve is often helpful in the establishment of the diagnosis.

Rheumatic pericarditis sometimes presents a picture confusingly similar to a. n. p. In such cases there are usually other signs of rheumatic fever: affection from the joints, from the myo- and endocardium with prolongation of conduction time and QRS changes. The course is often more prolonged, the pain is as a rule less predominant and the antistreptolysin titre is usually high.

Tuberculous pericarditis runs a more malignant and protracted course with little or no pain: the pericardium often shows massive effusion and careful search will usually reveal signs of active or earlier tuberculous lesions elsewhere in the body.

Purulent pericarditis, a now uncommon condition, is due to spread of a pyogenic infection elsewhere in the body.

Non-rheumatic myocarditis sometimes offers differential-diagnostic difficulties. The electrocardiographic abnormalities usually regarded as specific for pericarditis probably also indicate involvement of the myocardium, and it is possible that in some cases non-rheumatic myocarditis may be of one and the same etiology as a. n. p. This type of myocarditis is, however, malignant and unlike a. n. p. is often complicated by cardiac insufficiency. Moreover, non-rheumatic myocarditis claims a high mortality (Biörck, Gydell, Winblad — to be published).

The *etiology* of a. n. p. is unknown. The widely differing course of the disease from one case to another suggests that the condition can be caused by more than one agent. The theory most widely embraced is the one assuming viral infection of the pericardium. Culture of material from the pericardium has never been known to give bacterial growth. The fact that the condition is often preceded by infection of the upper respiratory tract argues for viral infection. Several cases of pericarditis in connection with viral pneumonia are on record. Finkelstein and Klainer (1944) described 3 cases. In 11 of the present series, cold agglutination tests gave a positive reaction in only 1.

The clinical picture of the condition contains many traits seen in Bornholm disease, which is sometimes complicated by pericarditis (Bing 1933, Hockstetter 1933, Dalsgård-Nielsen 1933, Aagard-Jensen 1952). Both diseases are characterized by a benign course, tendency to recurrence, and severe abdominal, chest and shoulder pain. Pleurisy is common in both. The abdominal pain may be attributable to peritoneal serositis. Warburg pointed out that epidemic myalgia might be a type of polyserositis (cit. from Gormsen, 1952). The Coxsackie-virus has often been demonstrated in Bornholm disease, but in none of his 5 cases of a. n. p. could Friedman (1952) demonstrate this virus. One of the most typical cases (no. 22) in the present series was studied for C-virus which could, however, not be shown. The increased frequency of a. n. p. in Malmö in 1952, may have been related to the relatively high frequency of C-virus infections — but not of myalgia epidemica type — during the latter part of the summer and autumn that year. In the present series however the cases did not seem to be related to any particular season and therefore permit no conclusions as to the possible relationship between a. n. p. and C-virus infections.

Treatment of acute, non-specific pericarditis is symptomatic. No specific therapy is available, although good results have been obtained with aureomycin (Taubert, Haus and Brams, 1950). It is, of course, difficult to judge the value of treatment in a disease with such a benign course. Neither aureomycin nor any other antibiotic produced any striking effect in the present series.

Prognosis. The primary prognosis is good, and Mac Cord and Taguchi's case referred to above is the only fatal case on record.

As already mentioned, the electrocardiographic changes are due at least partly to the extent of subepicardial myocarditis. The electrocardiographic changes usually disappear within 2 months, but if the myocardial affection has involved the deeper tissues it may become clinically manifest and can occasionally lead to progressive or even permanent myocardial damage. Godfrey (1951) described 5 cases of a. n. p. with clinical and electrocardiographical signs of myocardial injury 7 months, 1 year

and 2½ years respectively after the onset and expressed the view that the prognosis of this disease should not be regarded as undecidedly good. Pohl (1951) described 1 case in which the inverted T waves persisted even 8 months after the onset of pericarditis.

It has often been discussed whether acute, non-specific pericarditis — especially of the recurrent type — is capable of causing later chronic constrictive pericarditis. Levy and Pattersson (1950) reviewed 17 cases in patients who had been followed up for 6 months to 16 years (average 2 years) and in no instance did they find electrocardiographical or other evidence of persistent myocardial injury. Carmichael et al. (1951) reviewed 41 patients, 12 of whom had been followed up for more than 10 years. No electrocardiographical changes were observed. In one of the patients the X-ray appearance of the heart shadow suggested chronic pericardial changes. Freilich (1952), however, described a case of recurrent *a. n. p.* with roentgenographical and electrokymographical signs of a fibrous or adhesive pericarditis and expressed the view that this represents a precursory stage of constrictive pericarditis. He believes that this complication has never before been described.

In 2 cases¹ the onset of acute, and apparently non-specific, pericarditis was followed by the development of a picture of chronic, constrictive pericarditis. Both of the patients were operated on 6 months and 20 months respectively after the acute onset and with excellent results and microscopic examination of the operative specimen showed no signs of specific inflammation. These 2 cases are briefly described below.

G. R. (Born 14. 3. 1912.) A man, aged 40, who had always felt well, was troubled in December 1950 by a cough, undue fatigue on exertion and a transient seizure of precordial pain, but he was still able to carry on with his work. In January 1951 he had a cold with elevation of temperature (38–39° C). After 14 days' bed rest at home he returned to his work. On February 20, *i. e.* 1 week after return to work, he suddenly became ill with pain across the epigastrium, which was accentuated on deep respiration especially when lying flat. He therefore sat up all the first night. The following day the pain shifted up towards the precordium and to the entire left half of the chest and radiated out to the left shoulder. The temperature was then 38–39° C. The patient remained at home for 3 weeks. The severe pain disappeared after 2–3 days, but a mild, diffuse aching across the chest persisted. He had a mild, practically non-productive cough. He had no joint pain.

On March 14, 1950, the patient was admitted to hospital where *Pericarditis exsud. benigna non specifica* was diagnosed. He was pale and looked ill but had not cyanosis, dyspnoea or oedema. An inconstant rub(?) was heard over the lower part of the sternum. Blood pressure 130/80 mm Hg. The liver was palpated 1–2 cm below the arcus costarum. W. B. C. 7,100. He had low grade fever for about 12 days. Erythrocyte sedimentation rate: 73 mm/hr. on admission, three weeks later it was 9 mm/hr. and afterwards normal. The tuberculin reaction was positive (+ 0.1 mg), and the antistreptolysin titre determined on various occasions was always low.

X-ray examination of March 15 showed considerable general enlargement of the heart (850 cc/m² body surface) but no pulmonary changes. The electrocardiogram traced on March 14 showed no ST changes. All the T waves were positive, but T₁ was low.

On March 30 — one week after admission — the venous blood pressure was 20 cm and

¹ Case Nr. 14 and one case not included in the diagrams.

the liver was palpated 4–5 cm below the arcus costarum. Gradual improvement was then noted and the venous pressure decreased to 17 cm and the enlargement of the liver gradually subsided. About 1 month after admission the patient reported stab-like pain in the region of the precordium and a distinct friction rub was now audible. After a further 5 days the patient was symptom-free and since then no friction was heard. The patient was sent home on May 4, and then there was slight persistent enlargement of the liver, venous pressure was 20 cm but he felt well and showed no signs of oedema. The blood pressure was 105/85 cm Hg.

X-ray examination. The enlargement of the heart shadow, which was considerable on admission (850 cc/m²) gradually decreased: already by March 29 the heart had diminished considerably and on release on May 4, 1951, the heart was only moderately enlarged (590 cc/m²) and pulsations were regular and almost of normal size. The chest X-ray still showed no signs of a pathologic condition.

Electrocardiographical examination. As at the first examination, at which the electrocardiograph was normal except for a low T wave lead 1, the tracing taken 1 week later (March 21) showed inversion of T1, T2 and T3, while T4 was still positive.

When released on May 4, venous pressure was increased and later increased further to 23–25 cm but no tendency to oedema was noted. He was troubled by dyspnoea and epigastric pain on exertion and sometimes by precordial pain and headache, which increased in intensity when he bent forward and sometimes when he coughed. The electrocardiographic tracing taken on June 4 now showed a positive T1, which remained so, while T2 and T3 remained negative. PQ and QRS were normal throughout the entire observation period.

On March 26 the volume of the heart was 510 cc/m²: it had thus decreased. No pulsations were now detectable over the apex of the heart and pulsations on both the left and right sides were weak.

Constrictive pericarditis was assumed and the patient was referred to Malmö general hospital for investigation and, if indicated, surgical treatment. *On admission.* — He did not look ill, there was no oedema but the neck veins were distended. Auscultatory findings were normal. Blood pressure 120/95 cm/Hg. Heart beat: 88/min. The liver was palpated 3 cm below the arcus costarum and the venous pressure was increased — 30 cm. The diagnosis of constrictive pericarditis was established by the typical shape of the curves seen on heart catheterisation. On October 24 the patient underwent pericardiectomy (Prof. H. B. Wulff) at which a 3–4 mm thick layer of hard but not calcified pericardial tissue was removed. Histologic examination of the operative specimen showed connective tissue extremely rich in collagen but poor in cells: the connective tissue showed organised fibrin without signs of tuberculosis or other inflammation (Winblad).

The result of the operation was excellent. Venous pressure returned to normal, all symptoms disappeared. When last seen in 1953 the patient felt well and examination revealed no signs of incompenation. Venous pressure was now 10 cm. The electrocardiogram was normal and X-ray examination of the heart showed a normal size (vol. 420 cc/m²).

Comments. In this case the acute onset preceded by infection of the upper respiratory tract was typical of acute pericarditis. The cough and transient precordial pain 3 months earlier suggest that the patient had an attack at that time. No signs of earlier or active tuberculosis could be demonstrated. Chest-X-ray films taken on various occasions never showed any signs of a pathological condition. Joint pain was denied and on no occasion did the electrocardiograph show PQ changes suggestive of rheumatic etiology. The antistreptolysin titre was also regularly normal. A striking feature was the early clinical appearance of cardiac insufficiency, which was pronounced already 1 week after admission, when X-ray examina-

tion of the heart showed considerable enlargement, probably due to effusion in the pericardium. There may thus have been a certain degree of heart tamponade in this stage. As the cardiac enlargement subsided the return of the S. R. towards normal was at first accompanied by a certain decrease in the severity of the symptoms of cardiac insufficiency, but symptoms of impaired venous return to the heart soon increased again. Pericardectomy was done some 20 months after the onset of the condition. Histologic examination of the operative specimen showed no signs of specific inflammation in the pericardium.

Case 14 O. S. A man, aged 51, who denied earlier heart trouble, entered hospital on Feb. 8 complaining of recent (1 month) shortness of breath on exertion, palpitations, non-productive cough and «a feeling of fever». He denied chest pain. Mass chest X-ray had revealed enlargement of the heart but no pulmonary changes. He was medicated with digitoxin, which, however, produced no improvement. On May 2 he was examined by his doctor who noted a precordial friction rub at the left sternal border and a sedimentation rate of 102 mm. On admission to hospital on February 8 the patient did not feel ill, but he was slightly dyspnoeic. There was no oedema and the liver could not be palpated. Auscultatory findings were normal. No friction rub was heard now or later. Heart beat 104/min. Blood pressure 130/100. W. B. C. 5,100. Sedimentation rate 94 mm/hour.

X-ray examination on Feb. 9. Enlargement and increased roundness of the outline of the heart. Vol. 610 cc/m². On either side the hilus glands showed calcification. The lung fields were of normal appearance and showed no signs of stasis. The electrocardiograph showed iso-electric S—T segments, slightly positive T1 and negative T2—3—4.

During the first 5 days the patient had low grade fever. He had a transient cough, but was otherwise symptom-free. He denied chest and joint pain. The heart beat was about 110/min. during the first week, after which it persisted at 100/min. for 2—3 weeks and then gradually returned to normal. The sedimentation rate, which was 94 mm/hr. on admission, decreased fairly rapidly and after 1 month it was 22 mm/hr, and after 7 weeks 14 mm/hr. After a transient increase to 26 mm/hr. it was again normal 3 months after admission. The antistreptolysin titre determined on 3 occasions was always normal. The tuberculin reaction to 1 mg was positive, but negative to 0.1 mg. Guinea-pig inoculation and culture of the gastric washings were negative. Blood culture gave no growth.

Check X-ray examination on March 5 showed no further change in the size of the heart, but signs of stasis had appeared in either lung field and pleural changes with effusion were seen bilaterally. The patient was still symptom-free, there were no signs of oedema but the liver was palpated just below the arcus costarum and on March 11 venous pressure was 18 cm. At the end of April, about 10 weeks after admission, oedema of the legs, enlargement of the liver and a venous pressure of 27 cm were recorded. Venous pressure persisted above 20 cm and oedema of the legs increased as soon as the patient was up. Digitalis produced no demonstrable response.

X-ray examination on March 20 showed regression of the pleural changes, but the appearance of the heart and lungs was the same as before. Kymography on April 8 showed very small pulsations on both sides, especially on the right. No pulsations were discernible at the site of the apex. The electrocardiogram, which on admission (Feb. 9) showed slightly positive T1, but negative T2—3—4, now (Feb. 13) showed negative T waves in all standard leads and in the chest lead V2—4—5—7, by Feb. 20 all of the T waves had become more negative after which there was a gradual regression and on June 7 T1 was again slightly positive, and the other T waves less negative than before.

As the symptoms of impaired venous return showed no tendency to subside, the patient was referred to the surgical department, where he underwent pericardectomy with the removal of thick, fibrous pericardial tissue (N. P. Bergh). Histological examination of the operative specimen showed very stram collagen connective tissue without demon-

strable infiltration of inflammatory cells or signs of specific inflammation. The lymph glands showed normal structure (G. Björkmann). The result of the operation was very good. Venous pressure returned to normal and the patient became symptom-free. When last seen the patient felt very well and showed no signs of cardiac insufficiency. Venous pressure was 11 cm. The heart shadow was normal (vol. 430 cc/m²). The electrocardiograph was normal except for a low T₂.

Comments. In this case the onset was less acute than usual, and was not associated with pain — this was the only case in the series in which pain was not present — and the temperature was never more than slightly increased during the time he was in hospital. The patient had felt ill one month before admission, but observations made in hospital suggested only a fairly transient acute infection with return of the temperature within 5 days and of the SR within 7 weeks: the electrocardiographic changes also showed slight regression. Examination revealed no signs of rheumatic or tuberculous affection — there were no joint pain, the antistreptolysin titre was not increased and electrocardiogram showed no changes of the PQ or QRS.

X-ray examination showed no pulmonary changes, guinea-pig inoculation with gastric washings was negative and the tuberculin reaction was weak. The patient was thus considered to have subacute non-specific pericarditis which within 6 months developed into constrictive pericarditis.

Little is known of the etiology of chronic constrictive pericarditis. Of altogether 158 operated cases reported by various authors (Harrington 1944, Paul Castleman and White 1948, Mortensen and Warburg 1948 and Chambless et al. 1951) tuberculous origin was demonstrated in 15—28 per cent, rheumatic fever was rarely or never demonstrated as the causal factor and most cases were etiologically obscure. Blalock and Burwell (1941), however, found positive evidence for tuberculosis in 13 of their 20 operated cases (65 per cent). In some cases the patients had on some earlier occasion had acute pericarditis (Paul, Castleman and White 1948). It was this that induced some workers in this field to doubt the regularity of the good prognosis of acute benign pericarditis. Our 2 cases described in detail suggest that acute «benign», non-specific pericarditis really can develop into chronic constrictive pericarditis, an observation that had hitherto not been confirmed. This suggests that the future course of the disease should be predicted with caution. It is not possible to explain why pericarditis should develop into constrictive pericarditis in some patients but not in others. It may be attributable to difference in reaction of the pericardium to one and the same causal agent or, as already mentioned, it may be ascribable to a special type of infection. But in many cases of chronic constrictive pericarditis the condition is not preceded by any known attacks of acute pericarditis. In certain cases it might be a question of silent tuberculous pericarditis — an old «burned out», tuberculous pericarditis is difficult or impossible to diagnose histologically — in other cases one might imagine a primarily benign, possibly non-specific abortive pericarditis leading later to chronic progressive pericardial changes. That such «sub-clinical», abortive non-specific forms of pericarditis do occur is apparent from case 13 as well as from the high frequency of chronic adhesive pericarditis in autopsy

series. Thus of 8,912 autopsies at the Mayo Clinic, Smith and Willius found 373 (4.2 per cent) cases of pericarditis and of these, 144 (1.6 per cent) were cases of adherent pericarditis. Seventy-one (49.3 per cent) of these 144 cases were of unknown origin.

Like a. n. p., chronic constrictive pericarditis is commonest in young males. In the largest series of surgically treated cases of chronic, constrictive pericarditis (Chambliss et al. 1951) on record, for example, 48 of the 61 cases were seen in men and the average age of the series was hardly 32. This is another aspect of the disease requiring elucidation.

Summary.

During the 10 year period 1943—1952 altogether 64 cases of pericarditis were seen at Malmö general hospital, of these, acute non-specific pericarditis was seen in 21, rheumatic pericarditis in 12, pyogenic pericarditis in 7, tuberculous pericarditis in 6, constrictive pericarditis in 6. Ten cases could not be assigned with certainty to any known type. Pericarditis secondary to uraemia, myocardial infarction and tumours were not included.

The symptoms observed in 24 cases of acute non-specific pericarditis are described, with special reference to differentiation of the condition from myocardial infarction. It is stressed that the condition is sometimes erroneously diagnosed as myocardial infarction.

The prognosis is usually good, although the possibility of prolonged or permanent myocardial injury or the development of constrictive pericarditis must be considered. Two cases are described in which acute non-specific pericarditis (although the onset was less typical in 1) developed into chronic constrictive pericarditis. Pericardectomy 6 months and 20 months respectively after the onset of the symptoms produced excellent results in both cases. Neither the clinical picture nor histological examination of the operative specimen suggested tuberculous or rheumatic etiology. The development of constrictive pericarditis after acute non-specific pericarditis has apparently never before been described.

References.

1. Andersen, W. T.: *Acta med. Scandinav.* 1948, 213, 47. — 2. Aagaard, S., Jensen, S., and Eskjaer, S.: *Nordisk Medicin* 1952, 48, 1409. — 3. Barnes, A. R., and Burchell, H. B.: *Am. Heart J.* 1942, 23, 247. — Blalock, A. and Burwell, C. S.: *Surg. Gyn. and Obst.* 1941, 73, 433. — 4. Bellet, S. and McMillan, T. M.: *Arch. Int. Med.* 1938, 61, 381. — 5. Bing, H. J.: *Acta med. Scandinav.* 1933, 80, 29. — 6. Carmichael, D. B., Sprauge, H. B., Wyman, S. M., and Bland, E. F.: *Circulation*, 1951, 3, 321. — 7. Chambliss, J. R., Jarozewski, E. J., and Brofman, B. L.: *Circulation*, 1951, 4, 816. — 8. Dalsgaard-Nielsen, T.: *Ugesk. læger* 1933, 95, 522. — 9. Engelfeldt, E.: *Svenska Läkartidningen* 1952, p. 81. — 10. Evans, E.: *J. Am. Med. Assn.* 1950, 143, 954. — 11. Finkelstein, D., and Klainer, M. J.: *Am. Heart J.* 1944, 28, 385. — 12. Freilich, J. K.: *Ann. Int. Med.* 1952, 37, 388. — 13. Friedman, S., Ash, R., Harris, T. N., and Lee, H. F.:

- Pediatrics, 9, 551, 1952. — 14. Gilley, E. W., Mc Cord, M. D., and Taguchi, J. T.: *Am. J. Med. Sci.* 1951, 222, 249. — 15. Godfrey, J.: *Ann. Int. Med.* 1951, 35, 1336. — 16. Gormsen, J.: *Ugesk. læger* 1952, 33, 1096. — 17. Harrington, S. W.: *Ann. Surg.* 1944, 120, 468. — 18. Heckscher, H.: *Acta med. Scandinav.* 1933, 80, 251. — 19. Hilden, T.: *Nordisk Medicin* 1952, 47, 111. — 20. Levy, R. L., and Pattersson, M. C.: *Am. J. Med.* 1950, 8, 34. — 21. Logue, R. B., and Wendkos, M. H.: *Am. Heart J.* 1948, 36, 587. — 22. Mortensen, V., and Warburg, E.: *Acta med. Scandinav.* 1948, 131, 203. — 23. Mc Cord, M. D., and Taguchi, J. T.: *Arch. Int. Med.* 1951, 87, 727. — 24. Nathan, D. A., and Dathe, R. A.: *Am. Heart J.* 1946, 31, 115. — 25. Noth, P. H., and Barnes, A. R.: *Arch. Int. Med.* 1940, 651, 291. — 26. Nay, R. M., and Boyer, N. H.: *Am. Heart J.* 1946, 32, 222. — 27. Parker, R. C., and Cooper, H. R.: *J. Am. Med. Assn.* 1951, 147, 835. — 28. Paul, O., Castleman, B., and White, P. D.: *Am. J. Med. Sci.* 1948, 216, 361. — 29. Pohl, A. W.: *Ann. Int. Med.* 1950, 32, 935. — 30. Porter, W. B., Clarke, O., and Porter, R. R.: *J. Am. Med. Assn.* 1950, 144, 749. — 31. Reeves, R. L.: *Am. J. Med. Sci.* 1953, 225, 34. — 32. Smalley, R. E., and Ruddock, J. C.: *Ann. Int. Med.* 1946, 25, 799. — 33. Smith, H. L., and Willius, F. A.: *Arch. Int. Med.* 1932, 50, 410. — 34. Taubenhaus, M. M., and Brams, W. A.: *J. Am. Med. Assn.* 1950, 142, 973. — 35. Tomlin, C. E., Logue, R. B., and Hurst, J. W.: *J. Am. Med. Assn.* 1952, 149, 1215. — 36. Wolff, L.: *New Engl. J. Med.* 1944, 230, 422. — 37. Wolff, L.: *New Engl. J. Med.* 1943, 229, 423. — 38. Vander Veer, J. B., and Norris, R. F.: *Am. Heart J.* 1937, 14, 31. — 39. Vander Veer, J. B., and Norris, R. F.: *J. Am. Med. Assn.* 1939, 113, 1483. — 40. Talmage, W. G.: *Am. Heart J.* 1945, 29, 623.
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Alkali-Stable Growth-Promoting Factors for *Lactobacillus* *Leichmannii* in Human Livers.¹

By

TOR PETTERSSON, GUSTAF ÖSTLING and RUBEN GORDIN.

(Submitted for publication September 14, 1953).

When, in 1948, vitamin B₁₂ had been isolated and found to have a good therapeutic effect in pernicious anemia it was believed that the antianemic principle of the liver had been discovered. As soon as one year later Jacobson & Bishop, and in 1950 Owren, however, emphasized that vitamin B₁₂ is not as potent as crude liver extract. Folic acid, folinic acid, thymine and desoxyribosides, which have an antianemic influence, are not present in liver extract in amounts sufficient to explain its superiority. Hence there is reason to assume that liver extract contains factors influencing pernicious anemia other than vitamin B₁₂.

Vitamin B₁₂ is destroyed when boiled with sodium hydroxide at pH 10. In 1952, Robinson, Williams & Brown showed that crude liver extract after this alkali treatment still contains a growth factor for *Lactobacillus leichmannii*. Östling & Nyberg (1953) demonstrated, too, the presence of this factor (alkali-stable factor I) and of another group of alkali-stable factors (alkali-stable factor II) for the same microorganism. Alkali-stable factor II has a growth-promoting effect also for *Lactobacillus casei*, *Leuconostoc citrovorum*, *Streptococcus faecalis* and *Euglena gracilis*. It has been demonstrated by clinical experiments that liver extracts containing these alkali-stable factors and no vitamin B₁₂ activity are effective in the treatment of pernicious anemia (Östling, Nyberg & Gordin 1953), and that these extracts possess extrinsic factor activity (Östling, Nyberg & Gordin 1954).

Pernicious anemia being very rarely encountered in persons under 20 years of age and seldom before middle age, we have undertaken this investigation in

¹ The livers employed in this investigation were obtained from the Department of Pathological Anatomy, Maria Hospital, the Institute of Pathological Anatomy, the Institute of Forensic Medicine, the Children's Clinic and the First Women's Clinic, University of Helsingfors.

order to find out whether the content of alkali-stable, growth-promoting factors for *Lactobacillus leichmannii* in the liver is reduced with age, since this would offer some explanation of the disposition for pernicious anemia of the age groups in question. In view of the encouraging results obtained by intravenous therapy with crude liver extract in cirrhosis of the liver (Labby & al. 1947, Ralli & al. 1949, Adlercreutz 1953) we have included some cases of this disease and of fatty infiltration of the liver in order to study the alkali-stable factors in connection with these conditions also.

Experimental.

All liver extracts were prepared from human livers obtained at autopsy not later than 48 hours *post mortem*. The livers were refrigerated to -20°C . and finely ground. Dry substance was prepared from each powder by evaporation on a water bath at $35-38^{\circ}\text{C}$. for about 48 hours. 75 ml distilled water were added to 5 gm dry substance, and pH was adjusted to 7, after which 0.5 gm papain and 2.5 ml toluene were added. This mixture was kept for 24 hours at 38°C . When pH had again been adjusted to 7 the mixture was brought to the boil and filtered. The filtrate was used in the microbiological assays.

The alkali-stable liver factors for *Lactobacillus leichmannii* were determined by the routine method employed at the Pharmacological Laboratory of Messrs. Medica, Ltd. (Nyberg 1952). The extracts were investigated in amounts corresponding to 10^{-4} , 10^{-5} , 10^{-4} , 10^{-3} , 10^{-2} , $3 \cdot 10^{-2}$ and $6 \cdot 10^{-2}$ gm dry substance per test tube. All assays were carried out in duplicate. The extracts were assayed before and after boiling for one hour with sodium hydroxide at pH 10; the two growth curves thus obtained were identical. Bacterial growth was determined after incubation for 20 and 72 hours at 37°C . No bacterial growth was obtained with pure papain prepared in the same manner as described above.

The material for this investigation includes 49 livers from patients who had died from diseases other than pernicious anemia or diseases of the liver. These «normal» cases were classified in age groups as shown in Table I, in which the number of cases is also indicated. Furthermore our material includes 4 livers from persons with portal cirrhosis aged 41–80, 7 livers with incipient cirrhosis (49–71 years of age), 3 livers with fatty infiltration (29–64 years of age), and 3 livers with incipient fatty infiltration (55–77 years of age).

Table I.

Distribution of the examined livers according to age and diseases of the liver.

	«Normal» livers						Cirrhosis hepatis	Cirrhosis hepatis incipiens	Infiltratio adiposa hepatis	Infiltratio adiposa hepatis incipiens
Years	Below 0	0–1	1–20	21–40	41–60	61–80	41–80	49–71	29–64	55–77
No. of livers	7	11	3	8	6	14	4	7	3	3

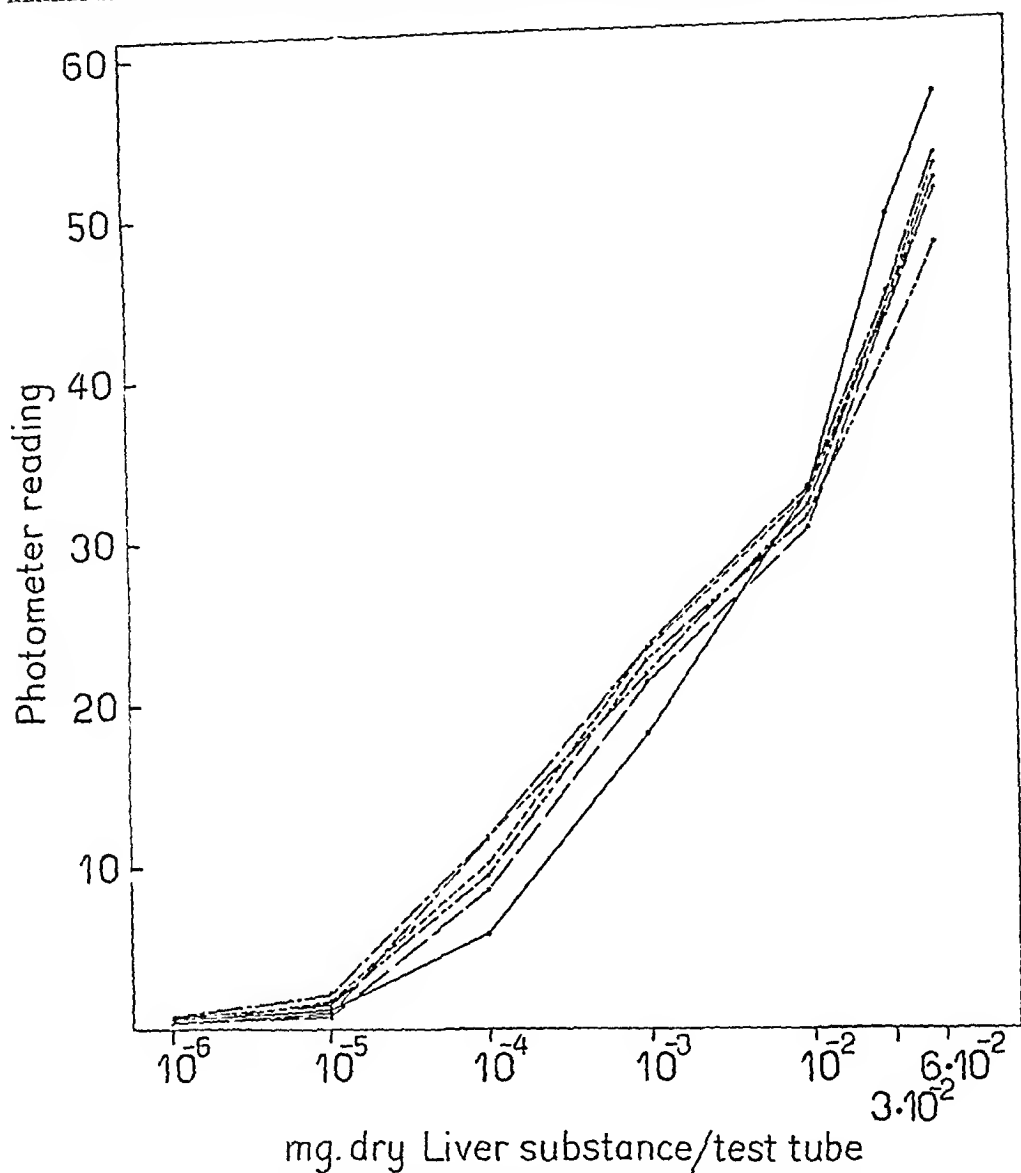


Fig. 1. Growth curves for *L. leichmannii* with liver extracts prepared from «normal» human livers from different age groups. 72 hours incubation.

Age group	Below 0 years	_____
0—1	„	_____
1—20	„	_____
21—40	„	_____
41—60	„	_____
61—80	„	_____

Bacterial growth after incubation for 72 hours with extracts of «normal» livers from the various age groups appears in Fig. 1. The curves for the age groups 0—1, 1—20, 21—40, 41—60 and 61—80 years do not differ much. The growth

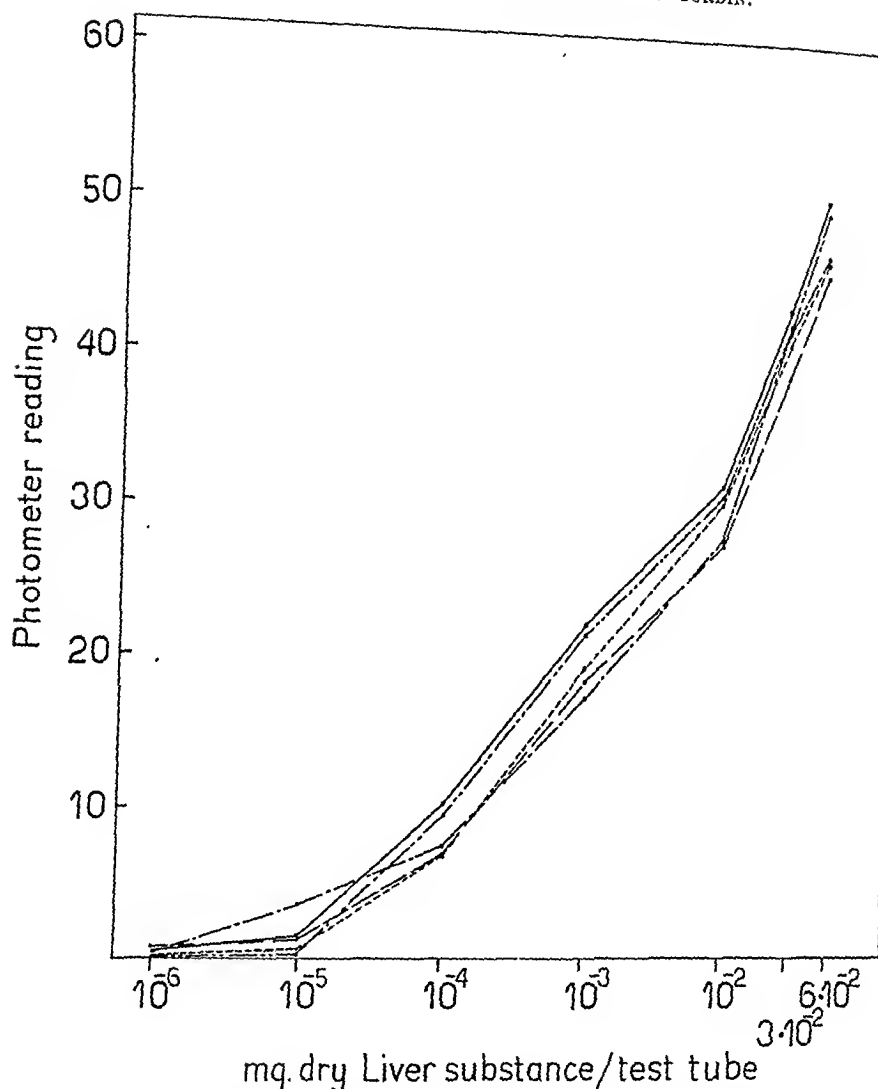


Fig. 2. Growth curves for *L. leichmannii* with liver extracts prepared from cirrhotic livers and livers with fatty infiltration. 72 hours incubation.

«Normal» livers —————
 Cirrhosis hepatis —————
 Cirrhosis hepatis incipiens —
 Infiltratio adiposa hepatis - - - - -
 Infiltratio adiposa hepatis incipiens - - - - -

curve for liver extract from foeta (the age group under 0 year), on the other hand, shows a somewhat different course. The bacterial growth with small amounts of liver extract is smaller in this group than in the others. At 10^{-2} gm liver per test tube the curves coincide, but after this the growth curve with foetal extract

shows a steeper rise than the rest. In Fig. 2 the growth curves with extracts from cirrhotic and adipose livers are compared with a mean curve made on the »normal» cases aged 0—80 years. It appears that the content of alkali-stable factors in the cirrhotic livers in the range 10^{-1} — 10^{-3} gm liver per test tube is about 25 per cent, and in the range 10^{-2} — $6 \cdot 10^{-2}$ about 10 per cent smaller than in normal livers. The differences are statistically significant at all points at the 5 per cent level of probability. It appears in Fig. 2 that the curves with extract from livers with incipient hepatic cirrhosis and fatty infiltration lie between the curves obtained on the normal cases and those obtained on cases with severe cirrhosis. The content of alkali-stable factors seems to be somewhat reduced in these cases, too.

Discussion.

The results of this investigation show that liver extracts prepared from human livers contain alkali-stable growth factors for *Lactobacillus leichmannii*. The content is the same in »normal» livers from all age groups from 0 year upwards. Any relationship between the alkali-stable factors, which are also antianemic (Östling, Nyberg & Gordin 1953, 1954), and the disposition for pernicious anemia of the middle-aged has thus not been established.

When comparing the growth curve for liver extract from foeta with the other curves in Fig. 1 it is found that it has a different course with amounts of dry liver substance smaller than 10^{-2} gm per test tube; according to Östling & Nyberg (1953) this may be attributable to a smaller content of alkali-stable factor I, or to the absence of this factor. From 10^{-2} gm liver per test tube upwards the foetal curve rises somewhat more abruptly than the others, which may indicate that alkali-stable factor II is present in larger amounts.

The results of the assays with extracts from cirrhotic livers (Fig. 2) show that these contain about 25 and 10 per cent less of the alkali-stable factors than »normal» livers in the ranges for factor I- and factor II-activity, respectively. Thus it seems possible that the alkali-stable growth factors are connected with the development of cirrhosis of the liver.

It is a noteworthy fact that no alkali-labile vitamin B_{12} effect was demonstrable in any of the liver extracts examined. This may be due to vitamin B_{12} either becoming alkali-stable, being destroyed, or otherwise becoming inactive for *Lactobacillus leichmannii* during the process of preparation.

Summary.

Human livers contain alkali-stable, growth-promoting factors for *Lactobacillus leichmannii*; the content is the same in livers from all age groups. On the other hand it is somewhat reduced in cirrhotic livers.

References.

- Adlercreutz, E.: *Nord. Med.* 50, 1634, 1953. — Jacobson, B. M. & Bishop, R. C.: *J. Clin. Invest.* 28, 791, 1949. — Labby, D. H., Shank, R. E., Kunkel, H. G. & Hoagland, C. L.: *J. A. M. A.* 133, 1181, 1947. — Nyberg, W.: *Acta med. Scandinav. suppl.* 271, 1952. — Owren, P. A.: *Scand. J. Clin. & Lab. Invest.* 2, 241, 1950. — Ralli, E. P., Leslie, S. H., Stueck, G. H., Shorr, H. E., Robson, J. S., Clarke, D. H. & Laken, B.: *Medicine* 28, 301, 1949. — Robinson, F. A., Williams, B. W. & Brown, L. H.: *J. Pharm. Pharmacol.* 4, 27, 1952. — Östling, G. & Nyberg, W.: *Ibid.* 5, 46, 1953. — Östling, G., Nyberg, W. & Gordin, R.: *Acta med. Scandinav.* 145, 40, 1953. — Östling, G., Nyberg, W. & Gordin, R.: *Acta Haematol.* 1954, in press.
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From the IVth Medical Clinic, the Maria Hospital, University of Helsingfors (Head: Professor Bertel von Bonsdorff, M. D).

The Thyro-Hypophysial Syndrome.

I. The primary reaction of the hypophysial eye signs (including exophthalmos) to the treatment of thyrotoxicosis.

By

B.-A. LAMBERG.

(Submitted for publication September 14, 1953.)

The ocular phenomena occurring in association with disturbances of thyroid function are as a rule divided in two categories. Lid lag, lid retraction, difficulty in convergence, and a variety of exophthalmos are classified as *thyrotoxic* symptoms, whilst oedema and puffiness of the eye lids, obliteration of the upper orbito-palpebral sulcus, chemosis, and conjunctival congestion, which are characteristic of the so-called progressive or malignant exophthalmos, have been called *»thyrotropic»* phenomena. The latter group has been thoroughly studied by many investigators, the malignant form of exophthalmos being a problem of great theoretical as well as practical interest. In view of Mulvaney's (48) observation that the histological changes encountered in the retrobulbar tissues belong to either of two different types, some writers have distinguished between a *»thyrotoxic»* and a *»thyrotropic»* variety of exophthalmos (2, 30, 48, 49, 56). Others, however, hold that there is only one form, in which different stages of development display different features (7, 10, 17 a, 19, 41, 42, 44, 51, 54, 58, 59, 61). This unitarian view is strongly supported by Rundle & Pochin's (58), Rundle & Wilson's (59, 60, 61) and Falconer & Alexander's (17 a) histological and volumetric investigations, and by Copper's (8), Means & Stanbury's (46) and Kearns, Henderson & Haines's (28) orbitonometric studies.

Malignant exophthalmos is associated with disturbances of thyroid function in various ways. It may be the first sign of thyrotoxicosis, or it may occur simultaneously with this condition. Most frequently it is, however, encountered when thyrotoxicosis has been relieved either by thyroidectomy or by irradiation or anti-thyroid therapy. Malignant exophthalmos may be produced in humans also by

treatment with thyrotropic preparations (66, 69). In regard of clinical phenomena and histological changes, the »thyrotropic» variety corresponds well to the experimental exophthalmos produced in animals by the treatment with thyrotropic preparations, by thyrostatic therapy, or by thyroidectomy (13, 62 c).

A fact apparently not universally known is, however, that a very large proportion of thyroidectomized patients react with an increase of the exophthalmometer values independently of whether any ocular signs have been initially present (11, 13, 14, 52, 65). Frequently the change is not observable when the patient is examined with the naked eye, since lid lag and lid retraction may have disappeared and the impression is thus conveyed that the eye has, on the contrary, gone inwards. A similar increase of the exophthalmometer values sometimes accompanies preoperative iodine treatment, thyrostatic therapy or irradiation of the thyroid gland (5, 9, 10, 13, 14, 34, 36, 37, 38, 40). Dobyns (13) emphasized that he had not found any relationship between the increase of the exophthalmometer values and the initial readings.

Since the literature dealing with these problems is very extensive, the reader is referred to the excellent surveys by Sattler (62), Means (43, 44), Mulvany (48), Mann (41), Dobyns (13), Danis & Mahaux (10) and Duke-Elder (16 a).

The purpose of the present investigation has been to ascertain whether there is any relation between the clinical eye signs initially present (lid lag, lid retraction, oedema and puffiness of the eye lids, filling or obliteration of the upper orbito-palpebral sulcus, etc.) and the occurrence of clinical and exophthalmometric eye reactions in immediate connection with the treatment of thyrotoxicosis. The intention is also to follow the development of the eye reactions for some years in order to find out whether the eye symptoms initially present and the type and degree of the immediate reaction are somehow correlated with a malignant exophthalmos occurring later, it being known that this condition may develop even five or more years after a thyroidectomy. This aspect of the problem is of great practical interest, but on account of the short period of observation the present paper deals only with the relationship between the immediate or primary reaction and the symptoms present prior to treatment.

Material.¹

The material includes 57 patients with thyrotoxicosis, 52 of whom were females and 5 males. The presence of lid lag, lid retraction, oedema or puffiness of the eye lids, filling or obliteration of the upper orbito-palpebral sulcus by a soft protuberance, conjunctival congestion, chemosis, lacrymation and ophthalmoplegia was recorded. The signs —, +, ++, +++ and ++++ were used to denote the degree of severity of these phenomena. Cases with oedema (Enroth's sign (17)) or puffiness of the eye lids (Vigouroux's, Sattler's sign (62, 70)), here commonly

¹ I have been kindly invited to examine patients also from the Surgical Department (Head: Prof. P. Tuovinen, M. D.) and from the Municipal Medical Department (Head: Docent G. Tötterman, M. D.) of the Maria Hospital, for which I wish to express my gratitude.

called swelling, and *suleus* phenomena (Posey & Spiller's sign (55)) of the degree ++ to +++ correspond to what Means's has called the hyperophthalmopathic form of Graves's disease (44, 45), the degree +++ being very severe malignant exophthalmos. +++ was, however, the severest form encountered in this investigation. The exophthalmometer values (EOV) were determined by exophthalmometry (EOM, see below) during periods varying from some weeks to six months. During the first stage of the treatment EOM was performed with intervals of two to five days. At the time when thyroidectomy was performed, or if a change in EOV had been observed, determinations were more frequently performed, viz. with intervals of one to three days. When the level had again become stationary after a thyroidectomy or during thyrostatic therapy the intervals were prolonged. Forty-one patients were treated with subtotal thyroidectomy. Preoperatively potassium iodide was administered, sometimes in conjunction with propylthiouracil (PTU) or 1-methyl-2-mercaptoimidazol (MMI). Sixteen cases were treated medically with PTU or MMI with or without iodide. In one case the thyroid was also irradiated. Wahlberg (74) showed that, in Finland, goitre is nearly always of the multinodular type. The findings in the present material are in good agreement with this, multinodular goitre being present in 53 cases and diffuse goitre in one case only.

Exophthalmometry.

A Hertel exophthalmometer was used. The technique was the same as with most exophthalmometers, record being taken of the position of the vertex corneae in relation to a frontal plane traversing both the lateral orbital margins. Owing to individual anatomical differences it is natural that the absolute exophthalmometer values are not significant. Using Hertel's exophthalmometer, the normal variation ranges between 10 and 24 mm (8, 9, 16, 32, 62, 65). In view of this, the adequacy of the denomination exophthalmos is debatable until the upper limit of the normal variation has been exceeded. It has been established, that in thyrotoxicosis, EOV lies on a higher level than normal (8, 9, 22, 28), but in regard of a single value this observation warrants no deductions unless the associated clinical signs are noted. Relative changes during the course of the treatment are highly significant, on the other hand, as was pointed out by Sattler (62). Occasional readings are, however, never to be relied on, fluctuations in EOV being demonstrable in normal eyes also. Frequent determinations are therefore required.

It should be emphasized that reliable results are obtainable only when all determinations are made by the same observer with the same instrument. The patient should fix his eyes on a point that on all occasions has approximately the same position relative to the eyes of the observer and to the horizontal plane of the exophthalmometer. The importance of this was established by the present author when, on the same day, a patient was examined also by another observer using another instrument; the results differed by 2 mm. Hence it is not advisable to send patients for EOM from a surgical or medical clinic to the outpatient department

of an eye clinic, where both the personnel and the instruments may vary. Another significant error inherent in this method of exophthalmometry is that due to the error of parallax. In the present investigation, which includes well over 10,000 readings, the patient was always told to fix his eyes on, and remember, some distinctive mark at the root of the nose or on the forehead of the observer; this was used as the point of fixation at the subsequent determinations also. It was attempted always to keep the eyes both of the patient and the observer in the same horizontal plane, and the exophthalmometer was also kept on the same plane as far as possible. It should, moreover, be borne in mind that the orbital margin is forwards concave, which may cause variations in the readings. Furthermore it is absolutely necessary to note the intermarginal distance that can be directly read on the frame of the exophthalmometer.

It appears from the above that exophthalmometry with Hertel's exophthalmometer is rather crude as a method. This impression is confirmed when successive determinations are made on the same occasion. As a rule I have therefore taken 6 to 10 readings each time and noted the mean value of these. The mean values for both eyes have been united to a curve (EOV curve). It was also found that the patient and the observer must get adapted to each other; therefore the first series of readings has been omitted in many cases.

When evaluating the primary reaction in EOV the following criteria have been used. The reaction was regarded as positive when the EOV curve showed a definite change in shape (Fig. 2, Case A 2) and the arithmetical mean of the EOV of both eyes increased by 0.25 mm at least, or when the level shifted by 0.25 mm (Fig. 3, Case C 3), in the surgical cases within nine days after the operation and in those medically treated within six weeks from the beginning of the treatment. An increase by 0.25 mm was regarded as significant in view of the number of readings taken on each occasion (see above).

Results.

It has not been possible to unite the different EOV reaction curves into one owing to the fact that the determinations were not always performed on the same days relative to the beginning of the treatment or the performance of thyroidectomy; furthermore the curves show rather large variations with regard to shape and course. The results have therefore been compiled in Table 1.

It appears in this table that an increase of EOV occurred in about 72 per cent of all cases. The rate of reaction was about the same independently of the treatment, whether surgical or medical. This is in good agreement with Dobyns's (11, 13) and Dobyns & Haines's (14) results. On the other hand the reaction curves differed somewhat with regard to shape, as appears from the following.

In the thyroidectomized cases an increase in EOV quite often occurred preoperatively independently of whether KJ, thyrostatic preparations, or a combination of both had been given (Fig. 1, 2). This increase was often found to be one of the first signs of a beginning normalization of thyroid function; sometimes it

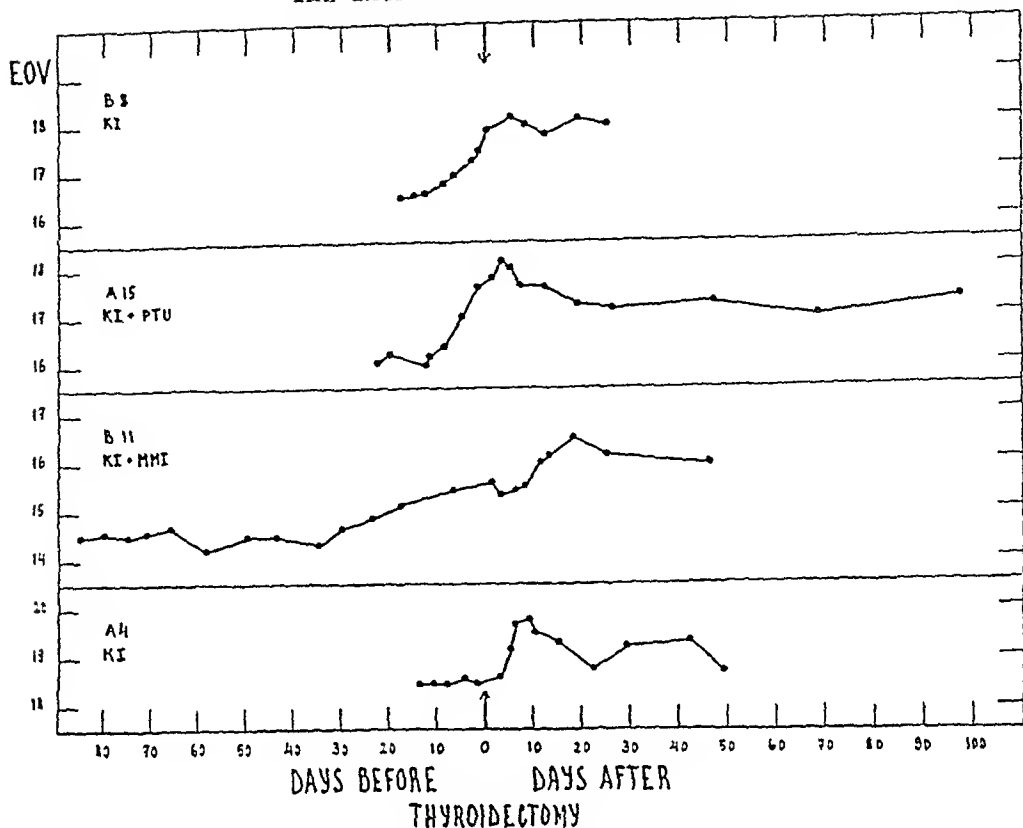


Fig. 1. The primary exophthalmic reaction to surgical treatment of thyrotoxicosis.

appeared simultaneously with an increase in cholesterol, a decrease in basal metabolic rate, and an improvement of the clinical state. It was also seen, as in Fig. 1 (cases B. 8 and A 15), that the preoperative treatment sometimes caused a maximal increase in EOY, and that no further increase was brought about by a subsequent thyroidectomy. In other cases there was a rapid, marked reaction within the first

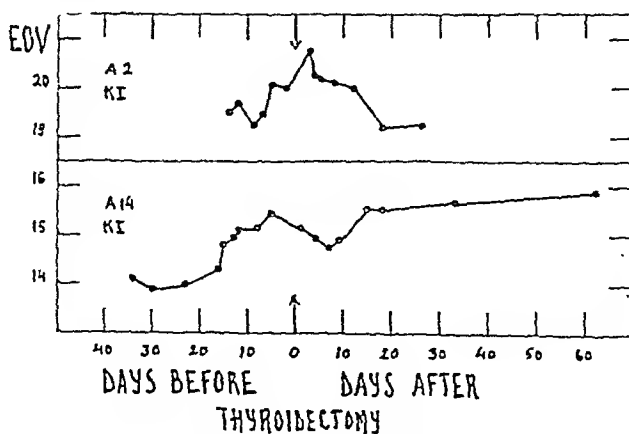


Fig. 2. The primary exophthalmic reaction to surgical treatment of thyrotoxicosis.

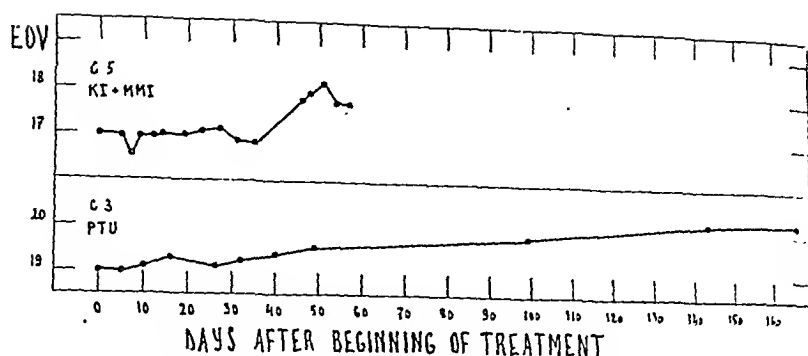


Fig. 3. The primary exophthalmic reaction to medical treatment of thyrotoxicosis.

days following the operation with a maximum within one to two weeks. This increase subsided either abruptly, or by steps during the first weeks; occasionally it persisted for long periods of time, or was even enhanced (Fig. 1, 2). When the therapy had been medical the reaction was often slower than after a thyroidectomy (Fig. 3).

On examining Table 1 it is, however, of particular interest to find that there was a reaction in as many as 30 of the 34 cases where swelling of the lids, or filling of the upper orbito-palpebral sulcus was present prior to treatment whereas, of the 23 patients who had none of these symptoms, 11 only had an increase in EOV. If the incidence is calculated as a percentage notwithstanding the small number of cases, the corresponding figures are 88 and 48 per cent.

Table 1.

The primary exophthalmic reaction following treatment of thyrotoxicosis.

Group	Treatment	No. of cases	No. of positive reactions	Incidence P. c.
Clinical eye signs (swelling of the lids and/or obliteration of the upper orbito-palpebral sulcus) present	Thyroidectomy (Group A)	24	21	
	Thyrostatic drugs (Group B)	10	9	
	Total	34	30	88
No clinical eye signs	Thyroidectomy (Group C)	17	8	
	Thyrostatic drugs (Group D)	6	3	
	Total	23	11	48
Entire material		57	41	72

When there was an increase in EOV it was frequently found that the upper orbito-palpebral sulcus gradually became filled by a soft protuberance in patients who had not previously shown this symptom, or that obliteration, when present, became more marked. Simultaneously the lids became somewhat puffy, and sometimes the lower sulcus, too, began to bulge, forward. The identification of the sulcus sign presents some difficulty, in particular in patients who normally have thick and somewhat flaccid lids. In these, however, any soft protuberance, characteristic of the sulcus sign, is not demonstrable by palpation. In some cases a rather firm, sausage-like protuberance was palpable in the upper orbito-palpebral sulcus, too; apparently it consisted of an enlarged portion of the lacrimal gland which protruded as a result of increased retrobulbar pressure (2, 50, 57). This sign was present only in patients with obliteration of the sulcus; it was found, for instance, in some cases of malignant exophthalmos. Increasing conjunctival congestion and lacrymation were also frequently observable. In some cases there was a subjective feeling of pressure behind the eyes and of tenseness in moving them, and a gritty sensation.

In Table 2 the differences in the initial exophthalmometer values and the differences in reaction between the two eyes of the same patient are demonstrated. It appears that an initial asymmetry by as much as 1.5 mm was not infrequent. The difference in reaction was as a rule less than 0.25 mm. In many cases it was, however, 0.26 to 0.50 mm, and in 3 cases it was more than 0.50 mm.

Table 2.

Asymmetry in initial exophthalmometer values and in the primary exophthalmic reaction following treatment of thyrotoxicosis.

Group ¹	Difference in exophthalmic reaction between the two eyes Range (Hertel readings)			Difference in initial exophthalmometer values between the two eyes Range (Hertel readings)		
	0—0.25	0.26—0.50	0.51—1.0	0—0.5	0.51—1.0	1.0—1.5
	No. of cases			No. of cases		
A	15	4	2	13	9	2
B	4	3	1	10	5	2
C	5	4	0	6	2	2
D	3	0	0	5	0	1
Total	27	11	3	34	16	7

It is seen in Table 3 that the severity of the clinical eye signs bears some relation to the EOV. The EOV varied rather much, however, and there is a great degree of overlap between the groups.

Discussion.

The results of the present investigation, which is only a part of the work to be carried out, deserve of certain remarks. It is noteworthy that *there is a marked*

¹ The classification in groups refers to Table 1.

Table 3.

*Distribution of initial clinical signs, exophthalmometer values and primary reaction to treatment of thyrotoxicosis.*¹

Severity of clinical signs	—	+	++	+++	++++
No. of cases.	23	24	6 (10)	4 (7)	(2)
Av. exophthalmometer value	16.4	17.4	20.7 (20.8)	20.0 (20.7)	(23.6)
Range of exophthalmo- meter readings	13.5—19.6	12.5—20.7	18.1—24.0 (18.1—24.9)	18.1—23.2 (18.1—23.2)	(19.0—23.2)
No. of positive exophthalmic reactions.	11	22	5	4	

difference in the rate of reaction between cases initially showing oedema or puffiness of the lids and/or obliteration of the upper orbito-palpebral sulcus, and those in which these symptoms are absent. It is difficult as yet to evaluate the significance of this observation, but it seems to suggest that every patient showing marked symptoms of this type may be suspected of developing malignant exophthalmos. The same view has been advocated by Means (43, 44), Paschkis & Cantarow (53), Copper (8), and Givner & Leiter (24), all of whom regard the presence of these signs in severe form as a general danger-signal. The significance of the sulcus sign as a manifestation of exophthalmos has been emphasized also by Rundle & Pochin (58) and Rundle & Wilson (60).

When comparing the clinical picture of the ocular reaction and that of malignant exophthalmos, the conclusion is reached that the difference between these two conditions is only one of degree. *The swelling of the lids and the filling or obliteration of the sulcus encountered initially in some cases of thyrotoxicosis constitute the same clinical picture as the changes occurring during or after the treatment of thyrotoxicosis. They resemble essentially, too, the changes typical of the so-called malignant exophthalmos, which the present author has also studied on a separate material not included here.* Similar results have been obtained by Copper (8) and Kearns et al. (28). According to these investigators the mean EOVS is higher than normal in thyrotoxicosis, and lies between the values of normal subjects and those obtained in cases of malignant exophthalmos. Kearns et al. emphasize that increased EOVS is associated with an increase in the retrobulbar tension in the orbit. I have observed that a high EOVS usually is associated with marked clinical eye signs. The fact that an increase of EOVS during and after treatment is accompanied by such symptoms is evidence in the same direction.

The etiology and pathogenesis of the ocular phenomena here concerned are not yet clarified. It has been assumed that diencephalohypophysial disturbances are

¹ The figure in brackets includes a number of cases not otherwise included in this investigation.

involved, and that the thyrotropic hormone of the hypophysis plays an essential part in these events (cf. Wahlberg (74), Means (43), Mann (41), Dobyns (13), Danis & Mahaux (10), de Gennes (23), Marchesani (42)). The effect of TSH on experimental animals lends substantial support to the view that a hypophysial factor is responsible for the phenomena in question. On the other hand it is by no means proved that TSH as such is the precipitating factor.

Repeated attempts have been made to elucidate this question by titration of the TSH level in various body fluids. The methods of determination of TSH have not been adequate enough, however, to warrant any definite conclusions. Most reliable are, perhaps, the investigations of Purves & Griesbach (55 a), who used guinea pigs, and of d'Angelo, Paschkis, Gordon & Cantarow (3), who employed the so-called tadpole method. The former found that the TSH level of the blood was high in most cases of malignant exophthalmos, whilst no TSH was detected in some. The latter were not able to demonstrate any difference in the content of TSH in the blood of normal persons and of patients with exophthalmos. Similar results have also later been obtained (17 a, 62 b). Even Friedgood (20, 21) emphasized the fact that the experimental form of exophthalmos is aggravated at the moment when the purely thyrotropic effect has subsided owing to the formation of antihormone; there did not seem to be any corresponding inhibition of the exophthalmic effect. Furthermore Dobyns (12) was able to demonstrate that the exophthalmic effect of purified TSH preparations was inferior to that of less pure preparations. Jefferies (27) observed that, on inactivation of the thyrotropic component *in vitro* by elementary iodine by the method of Albert et al. (1), the exophthalmic effect was sustained. This is in contrast to Dobyns & Rawson's (15) results; in similar experiments these investigators found, namely, that the ophthalmotropic component was also inactivated. Friedgood (20, 21), McCullagh, Ruedemann & Gardner (39), Purves & Griesbach (55 a) and Medine (47) advocated the view that exophthalmos is not caused by the thyrotropic component proper. Recently Thompson (67) and Forsham (18) have reported that Dobyns, in investigations not yet published, has succeeded in isolating an ophthalmotropic component. Asboe-Hansen, Iversen & Wichmann (4 b) have, however, titrated the TSH level in the serum in malignant exophthalmos and report that the content of TSH was increased in 9 cases of 10. Similar results were obtained by Savoie (62 a).

As previously pointed out it is difficult to decide in clinical practice whether a condition is properly called exophthalmos until EOY exceeds a certain limit. The initial clinical eye signs (oedema, puffiness, filling or obliteration of the sulcus, bulging of the eye lids, etc.) seem, for instance, to be much more significant than the initial EOY. An eye set in a narrow orbit and with protruding lateral orbital margins may display marked clinical signs of malignant exophthalmos even though EOY lies within the normal range. In particular it should be borne in mind that the denomination «thyrotropic exophthalmos» is evidently a misnomer, as appears from what has been said above. Though other fatty tissues respond to some extent, too, the adipose tissue of the orbit has a peculiar affinity for the exophthalmos-producing hypophysial factor, as Dobyns (12), Smelser (63) and Smelser &

Ozanic (64) have shown. In the rare, so-called localized myxoedema, which occurs under the same conditions as malignant exophthalmos (25, 31, 70 a, 76), oedema rich in hyaluronic acid is present just as in the retrobulbar adipose tissue in malignant exophthalmos (4 a, 35). The temporal and facial oedema described by Thompson & Thompson (68) and by Wahlberg (71, 72, 73) apparently belongs to the same group of phenomena. In one case in group B in the present series such oedema developed simultaneously with an increase in EOY and an aggravation of the clinical eye signs. The patient's face became more and more «Cushing-like». Irradiation of the hypophysis brought about a decrease in EOY and a relative relief of the clinical eye signs; simultaneously the temporal and facial oedema improved. *Obviously the phenomenon here concerned is not a hypophysial «exophthalmos», or hypophysial ocular manifestations alone, but a group of hypophysial symptoms which may develop in different parts of the body but are principally encountered in the retrobulbar tissues and in the eye region. It is a hypophysial syndrome, associated in some unknown way with disturbances in thyroid function, for which it is difficult to find an adequate name as long as the precipitating hypophysial factor has not been identified. The denomination thyro-hypophysial syndrome may be suggested.* Means (44, 45) has spoken of Graves's disease, classic Graves's disease or ophthalmopathic Graves's disease, and hyperophthalmopathic Graves's disease with or without thyrotoxicosis. The corresponding terminology would, then, be simple thyrotoxicosis, thyrotoxicosis accompanied by the thyro-hypophysial syndrome (of varying degrees), or thyro-hypophysial syndrome alone (without thyrotoxicosis).

With regard to the asymmetric or unilateral exophthalmos, sometimes occurring under the same conditions as the bilateral form (6, 16, 29, 34 a, 62), the following statements may be made. Some difference in EOY between the two eyes is present in a large number of cases (9, 16, 32), as was established in the present material also (Table 2). Wahlberg (75) suggested that the unilateral variety of exophthalmos is a type of the so-called Seebright-Bantam syndrome, in which the sensitivity of one end-organ (the eye) to its tropic hormone is impaired. In some of the present cases I observed a difference in degree of reaction between the two eyes, which lends support to this view (Table 2).

It is a fact deserving of some consideration that a maximal eye reaction is sometimes obtained preoperatively as a result of the preoperative (= medical) treatment. By a slow medical thyroidectomy, achieved by medical therapy, it is thus possible to bring about a maximal primary reaction in some cases; after this there is no additional reaction following thyroidectomy. Taylor, Large & Noth (66 a) treated thyrotoxic patients with propylthiouracil and observed in some cases a marked eye reaction. On some of these patients subtotal thyroidectomy was performed later, after which the rate and degree of reaction was much reduced. The results are interpreted as an indication for surgical therapy in cases with the clinical eye signs in question. It may, however, reasonably be assumed that the difference was due to the fact that the eyes had reacted maximally, or almost maximally, already prior to the operation. The reaction is slower than that following a surgical operation in many cases, as was observed also by Beierwaltes (5) and Lederer (33). This is of some significance in the treatment of cases showing marked ocular

phenomena, in which a disposition for malignant exophthalmos must be regarded as present. Dobyms (13) believes that the more rapidly a malignant exophthalmos develops the greater is the risk of the eyes being lost. Apparently on the same grounds Arauow et al. (4), Beierwaltes (5) and Mahaux (37) have recommended a thyrostatic therapy in the type of syndrome here discussed. This offers, moreover, in most cases the possibility of making the patient thyrotoxic again if the eyes are endangered. If a thyroidectomy has been performed there is, of course, no such chance. For the same reasons Hertz, Means & Williams, (26) Soley (65) and Soley & Stone (65 a) recommended irradiation of the thyroid in cases of this type.

It appears in Table 1 that signs of a thyro-hypophysial syndrome were initially present in 60 per cent of all cases. The significance of the clinical eye signs as a manifestation of hypophysial involvement in the development of the clinical state is evidenced by this and by the data given in Table 3. In the latter it is seen that an increase in the average EOV runs parallel with an aggravation of the clinical state. At all events the clinical picture seems to be a more reliable index than the initial EOV as far as individual cases are concerned. In the severest group (++++), for instance, EOV lies between 19.0 and 28.2, and there is a great degree of overlap between the different groups.

Summary.

The present paper is a part of an investigation on the ocular reactions and the development of exophthalmos in thyrotoxicosis. The results presented here relate to the primary ocular reaction during the treatment of thyrotoxicosis. Exophthalmometry was performed with a Hertel exophthalmometer. The clinical eye signs, chiefly oedema (Enroth's sign) and puffiness of the lids (Vigornx's, Sattler's sign), and filling or obliteration of the upper orbito-palpebral sulcus (Posey & Spiller's sign) were observed. The material includes 57 cases of thyrotoxicosis, of which 41 were treated by subtotal thyroidectomy and 16 were medically treated. It appears from the results that the exophthalmometer values (EOV) were increased by the treatment of thyrotoxicosis in about 72 per cent of cases. Simultaneously the above-mentioned clinical eye signs appeared, or were aggravated if already present. Postoperatively there was a maximal *primary reaction* within one to two weeks. In the cases showing oedema and puffiness of the lids and/or filling of the upper orbito-palpebral sulcus by a soft, palpable protuberance prior to treatment a reaction occurred in about 88 per cent of cases. In the others the rate of reaction was about 48 per cent. The significance of these results is discussed and it is emphasized that the risk of an increase in the exophthalmometer values on normalization of thyroid function may be estimated by observing the initial clinical eye signs. The pathogenesis of the ocular phenomenon and terminology are discussed; it is pointed out that the concept exophthalmos cannot be satisfactorily defined, and that the denominations hypophysial «exophthalmos» and, in particular, «thyrotropic exophthalmos» are not appropriate in view of the fact that the exophthalmic component has not yet been isolated. Furthermore it is pointed out

that the ocular phenomena in question apparently are only one aspect of a hypophyseal syndrome associated in some unknown way with thyrogenic disturbances and manifesting itself as oedema and puffiness of the lids, obliteration of the upper orbito-palpebral sulcus (and other eye signs accompanying malignant exophthalmos) varying in degree, local myxoedema, and temporal or facial oedema. The denomination *thyrohypophyseal syndrome* is suggested as a more adequate term.

A difference between the two eyes with regard to reactivity was demonstrable in some patients, which seems to suggest that the unilateral form of exophthalmos accompanying thyrogenic disturbances may be a manifestation of the Seebright-Bantam syndrome. Furthermore it is emphasized that the present results are evidence in favour of the view that what has been distinguished as *'thyrotoxic'* and *'thyrotropic'* varieties of exophthalmos are different degrees of the same phenomenon.

It is further emphasized that the degree of severity of the thyro-hypophyseal syndrome should be estimated principally on the basis of the clinical eye signs and not by the exophthalmometer values as far as individual cases are concerned. The significance of occasional exophthalmometer readings, few in number and taken under varying conditions, is doubted.

Addendum.

Whilst this paper was in preparation, B. M. Dobyns & S. L. Steelman (Endocrinology 1953: 52: 705) reported investigations on the relationship between the thyrotropic and exophthalmic effect of various thyrotropic preparations. They were not able to demonstrate any correspondence between these two reactions and allege this as further evidence in favour of the view that the exophthalmic factor is not identical with TSH.

References.

1. Albert, A., Rawson, R. W., Merrill, P., Lennon, B. & Riddell, C.: J. Biol. Chem. 1946: 166: 637. — 2. Andersson, B.: Acta med. scandinav. 1950: 137: 254. — 3. d'Angelo, S. A., Paschkis, K. E., Gordon, A. S. & Cantarow, A.: J. Clin. Endocrinol. 1951: 11: 1237. — 4. Aranow, H., Elliot, R. H. E., Frantz, V. K., Meleher, G. W. & Werner, S. C.: Ann. Surg. 1946: 124: 167. — 4 a. Asboe-Hansen, G. & Iversen, K.: Acta endocrinol. 1951: 8: 90. — 4 b. Asboe-Hansen, G., Iversen, K. & Wichmann, R.: Acta endocrinol. 1952: 11: 576. — 5. Beierwaltes, W. H.: Arch. Int. Med. 1948: 81: 364. — 6. Bonnet, P.: J. med. Lyon 1951: 32: 561. — 7. Brain, W. R.: Proc. Roy. Soc. Med. 1952: 45: 237. — 8. Copper, A. C.: An introduction to clinical orbitometry. Leiden 1948. — 9. Danis, P. & Mahaux, J.: Ann. endocrinol. 1951: 12: 656. — 10. Danis, P. & Mahaux, J.: Bull. Soc. Belge Ophth. 1951: 116. — 11. Dobyns, B. M.: Surg., Gyn. & Obst. 1945: 80: 526. — 12. Dobyns, B. M.: Surg., Gyn. & Obst. 1946: 82: 290, 609 and 717. — 13. Dobyns, B. M.: J. Clin. Endocrinol. 1950: 10: 1202. — 14. Dobyns, B. M. & Haines, S. F.: J. Clin. Endocrinol. 1946: 6: 633. — 15. Dobyns, B. M. & Rawson, R. W.: Endocrinology 1951: 49: 15. — 16. Drescher, E. P. & Benedict, W. L.: Arch. Ophth. 1950: 44: 109. — 16 a. Duke-Elder, S.: Textbook of Ophthalmology, vol. V: 5474. London 1952. — 17. Enroth, E.: Finska Läk.sällsk. Hndl. 1924: 66: 895. — 17 a. Faleoner, M. A. & Alexander, W. S.:

- Brit. J. Ophth. 1952: 35: 253. — 18. Forsham, P. H.: J. Clin. Endocrinol. & Metab. 1953: 13: 618. — 19. François, J.: Acta Ophth. 1951: 29: 423. — 20. Friedgood, H. B.: Arch. Ophth. 1940: 24: 1176. — 21. Friedgood, H. B.: J. Clin. Endocrinol. 1941: 1: 804. — 22. Galli-Mainini, C.: Ann. Int. Med. 1942: 16: 415. — 23. de Gennes, L.: Les maladies des glandes endocrines. Paris 1952. — 24. Givner, I. & Leiter, L.: Am. J. Ophth. 1950: 33: 623. — 25. Grynkewich, S. E., Laughlin, R. M., Herron, F. T. & Carmel, W. J.: Am. J. Med. Sc. 1951: 222: 142. — 26. Hertz, S., Means, J. H. & Williams, R. H.: West. J. Surg. 1941: 49: 493. — 27. Jefferies, W. M.: J. Clin. Endocrinol. 1949: 9: 927. — 28. Kearns, T. P., Henderson, J. W. & Haines, S. F.: Am. J. Ophth. 1953: 36: 45. — 29. Kisner, W. H. & Mahorner, H.: Surg., Gyn. & Obst. 1947: 84: 326. — 30. Klotz, H. P.: Ann. Endocrinol. 1948: 9: 187. — 31. Klotz, H. P.: Ann. Endocrinol. 1949: 10: 597. — 32. Knudtson, K.: Acta psych. & neurol. 1949: 24: 523. — 33. Lederer, J.: Ann. Endocrinol. 1949: 10: 44. — 34. Lederer, J.: Ann. Endocrinol. 1949: 10: 166. — 34 a. Lederer, J. & Hambresin, L.: Ann. Endocrinol. 1951: 12: 73. — 35. Ludwig, A. W., Boas, N. F. & Soffer, L. S.: Proc. Soc. Exper. Biol. & Med. 1950: 73: 137. — 36. Mahaux, J.: Acta clin. belg. 1949: 4: 1. — 37. Mahaux, J.: Science med. prat. 1950: 1. — 38. Mahaux, J. & Delcourt, R.: Ann. endocrinol. 1949: 10: 463. — 39. McCullagh, E. P., Ruedemann, A. D. & Gardner, W. J.: Tr. Am. A. Study Goiter 1946: 15. — 40. McCullagh, E. P. & Sirridge, W. T.: J. Clin. Endocrinol. 1948: 8: 1051. — 41. Mann, I.: Ophth. Literature 1947: 1: 343. — 42. Marchesani, O.: Graefes Arch. f. Ophth. 1952: 152: 553. — 43. Means, J. H.: Am. J. Med. Sc. 1944: 207: 1. — 44. Means, J. H.: Ann. Int. Med. 1945: 23: 779. — 45. Means, J. H.: The Thyroid and its Diseases. Philadelphia 1948. — 46. Means, J. H. & Stanbury, J. B.: Am. J. Med. Sc. 1950: 220: 357. — 47. Medine, N. M.: Am. J. Ophth. 1951: 34: 1587. — 48. Mulvany, J. H.: Am. J. Ophth. 1944: 27: 589, 693 and 820. — 49. Mulvany, J. H.: Proc. Roy. Soc. Med. 1952: 45: 241. — 50. Naffziger, H. C.: Ann. Surg. 1938: 108: 529. — 51. Naffziger, H. C.: Am. J. Surg. 1948: 75: 25. — 52. Pagliarini, N. & Caviechi, L.: Riv. oto-neuro-oftal. 1950: 25: 153, abstr. in Ophth. Literature 1951: 4: No. 3073. — 53. Pasehki, K. E. & Cantarow, A.: J. Clin. Endocrinol. 1947: 7: 102. — 54. Pochin, E. E.: Proc. Roy. Soc. Med. 1945: 38: 669. — 55. Posey, W. C. & Spiller, W.: The eye and the nervous system. Philadelphia 1906, quoted by Mulvany 1944. — 55 a. Purves, H. D., & Griesbach, W. E.: Brit. J. Exper. Path. 1949: 30: 23. — 56. Reichling, W.: Ber. Dtsch. Ophth. Ges. Heidelb. 1950: 56: 279. — 57. Rose, E. & Mc Connell, J.: Am. J. Med. Sc. 1947: 213: 74. — 58. Rundle, F. F. & Pochin, E. E.: Clin. Sc. 1944: 5: 51. — 59. Rundle, F. F. & Wilson, C. W.: Clin. Sc. 1944: 5: 17. — 60. Rundle, F. F. & Wilson, C. W.: Clin. Sc. 1944: 5: 31. — 61. Rundle, F. F. & Wilson, C. W.: Clin. Sc. 1944: 5: 177. — 62. Sattler, H.: Handb. d. Ges. Augenheilk. 1909: 9: 1. — 62 a. Savoie, J.-C.: Ann. endocrinol. 1952: 13: 81. — 62 b. Simkin, B., Starr, P. & Hancock, C.: J. Clin. Endocrinol. & Metab. 1952: 12: 940. — 62 c. Smelser, G. K.: Am. J. Ophth. 1937: 20: 1189. — 63. Smelser, G. K.: Am. J. Path. 1939: 15: 341. — 64. Smelser, G. K. & Ozanics, V.: Am. J. Ophth. 1949: 32: 1557. — 65. Soley, M. H.: Arch. Int. Med. 1942: 70: 206. — 65 a. Soley, M. H. & Stone, R. S.: Arch. Int. Med. 1942: 70: 1002. — 66. Stallard, H. B.: Brit. J. Ophth. 1936: 20: 612. — 66 a. Taylor, N., Large, A. & Noth, P.: Am. J. Med. Sc. 1950: 220: 362. — 67. Thompson, W. O.: J. Clin. Endocrinol. & Metab. 1953: 13: 457. — 68. Thompson, W. O. & Thompson, P. K.: Am. J. Med. Sc. 1929: 178: 73. — 69. Thompson, W. O., Thompson, P. K., Taylor, S. G. & Dickie, L. F. N.: West. J. Surg. 1939: 47: 4. — 70. Vigoroux, R.: Progrès Méd. 1889: 15: 43, quoted by Mulvany 1944. — 70 a. Vilanova, X. & Canadell, J. M.: J. Clin. Endocrinol. 1949: 9: 883. — 71. Wahlberg, J.: Finska Läk.sällsk. Hndl. 1936: 79: 579. — 72. Wahlberg, J.: Finska Läk.sällsk. Hndl. 1937: 80: 813. — 73. Wahlberg, J.: Acta med. scandinav. 1938: suppl. 89. — 74. Wahlberg, J.: Acta med. scandinav. 1938: suppl. 94. — 75. Wahlberg, J.: Nord. Med. 1952: 48: 1117. — 76. Warburg, M.: Ugeskr. f. Laeg. 1949: 112: 673. — 77. Weekers, R. & Dedoyard, J.: Bull. Soc. Belge Ophth. 1951: 122.

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On the Significance of Peptic Digestion.

By

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The opinion of the relative importance of chemical and mechanical factors in gastric digestion has varied at different times. During the 19th and at the beginning of the 20th century the chief emphasis was placed on the chemical side of gastric function. It was held in particular that peptic digestion was of great importance for protein digestion and absorption. One cannot, however, envisage that the vitally important protein digestion could be so poorly provided for that lack of peptic digestion would cause disturbances. Peptic digestion is transiently or constantly deficient in a great many clinically otherwise healthy persons, *i. e.*, in persons with achlorhydria. In persons with acid gastric secretion, also, the gastric content usually attains a sufficient acidity to make peptic digestion possible to a sufficient degree only 1 to 1½ hours after a meal (*e. g.*, Brummer and Ruikka). In actual fact, protein digestion has never been found to be disturbed in achlorhydria if we use the total nitrogen absorption as an indication. This is well understood, since the enzymes of the trypsin group can digest native proteins without difficulty. After total gastrectomy, also, protein digestion is normal according to several investigators (MacDonald et al., Farris et al.); according to others some disturbances are, however, evident (Tomoda, Everson).

It was the object of the following study to observe whether, regardless of a normal total digestion, the lack of peptic digestion causes a delay in the first phase of protein digestion and absorption.

The glycine test of Christensen and Shwachman was used in the experiments. The test persons ingested 1.5 grams of gelatin per kilogram of body weight in 30 ml of warm water per kilogram. Venous blood was collected just before and 2, 3 and 4 hours after the feed. The glycine content of the blood samples was determined according to Alexander et al.

The first test group consisted of 21 persons with achlorhydria. Four of these suffered from pernicious anaemia. In the remaining 17 cases the diagnosis of achlorhydria was in 14 cases based on repeated histamine tests and in 3 cases on one

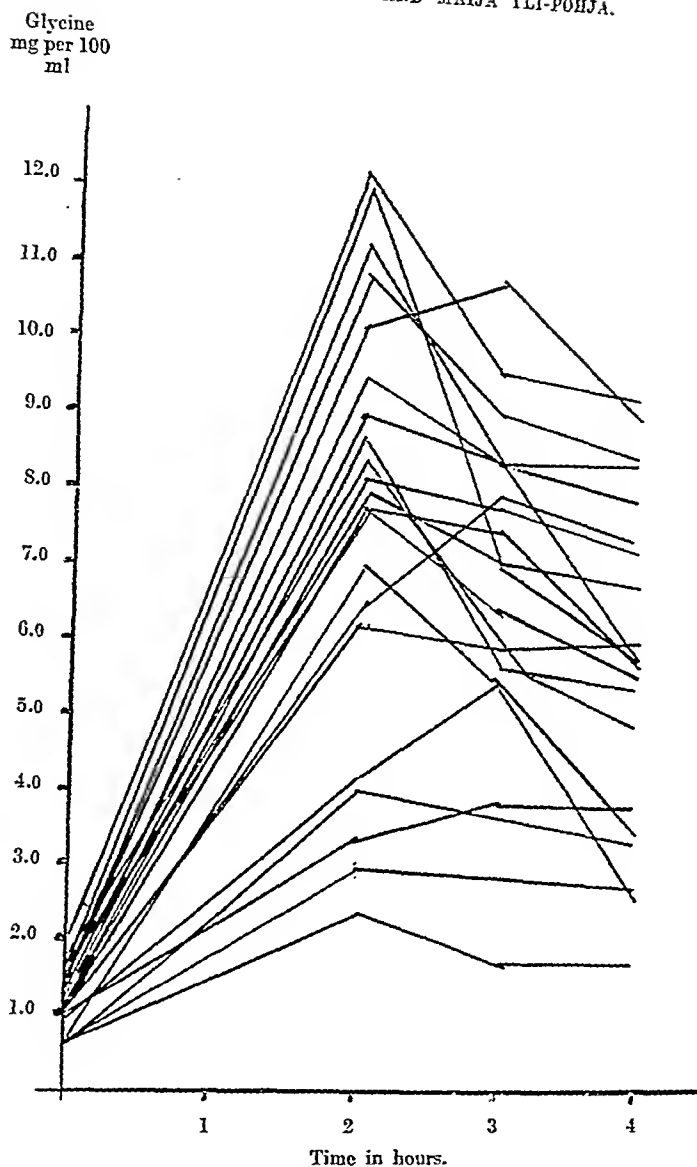


Fig. 1. Results of glycine test in persons with achlorhydria.

test only. The achlorhydric group comprised 14 women and 7 men, whose average age was 52 years.

The second test group consisted of 10 persons on whom subtotal gastrectomy had been previously performed for peptic ulcer. There were 2 women and 8 men, with an average age of 50 years.

Twenty persons (6 women and 14 men) with normal acid gastric secretion formed a control group, in which the average age was 43 years.

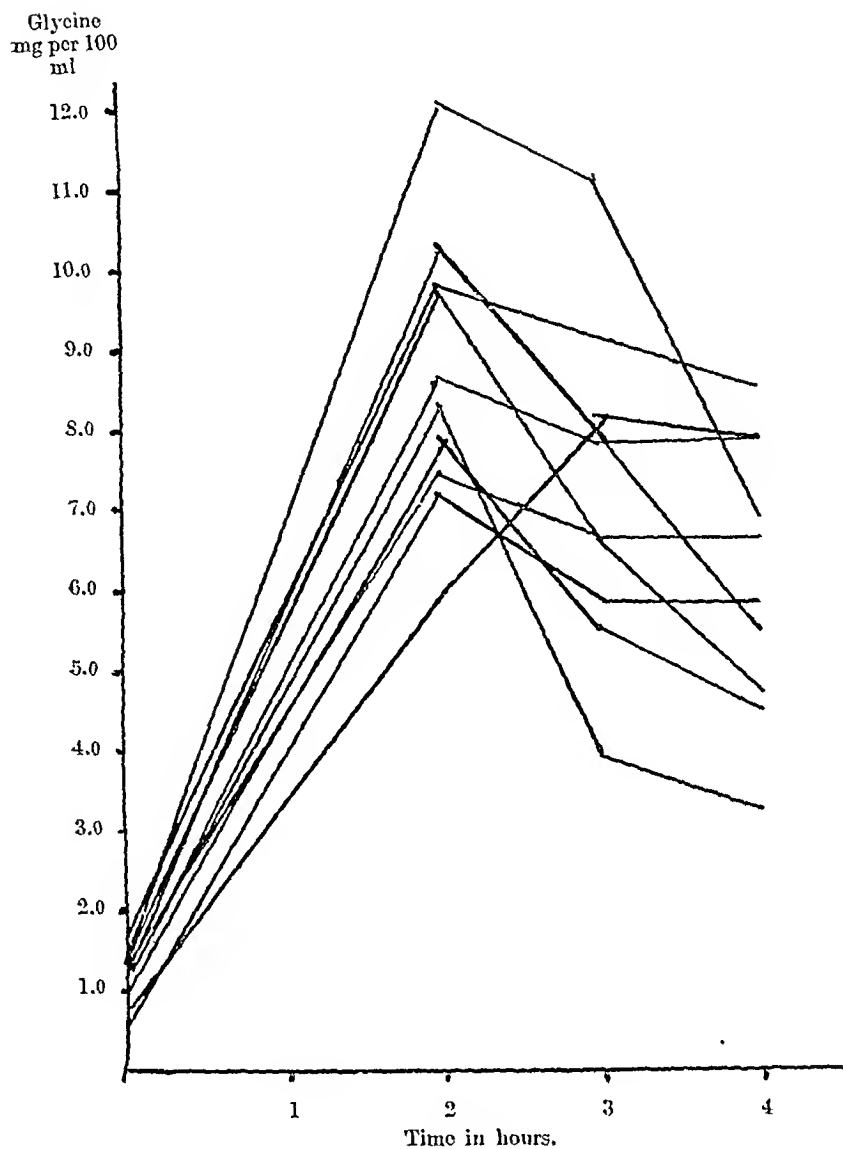


Fig. 2. Results of glycine test in persons with an earlier subtotal gastrectomy.

None of the test persons was affected with severe digestive or other organic disease.

Results and Discussion.

The results obtained in the different test groups are shown in Figs. 1—3 and the mean values for each group are given in Fig. 4.

No marked difference was seen in the mean values for the persons with achlorhydria and those with acid gastric secretion. In both groups the rise in the plasma

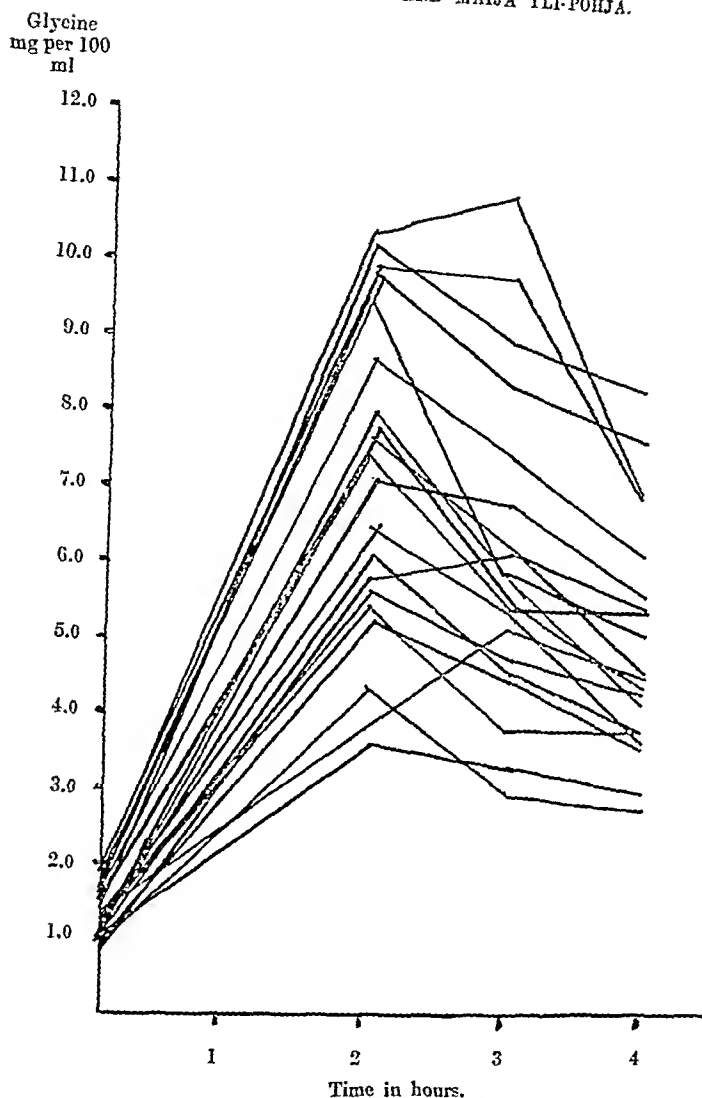


Fig. 3. Results of glycine test in persons with acid gastric secretion.

concentration of glycine 2 hours after ingestion of gelatine was the same. In individual cases the glycine level varied in persons with achlorhydria over a somewhat greater range than in persons with acid gastric secretion. Four hours after ingestion the glycine level appeared to be slightly lower in the achlorhydric group than in the other test groups. In view of the great range of dispersion of the glycine values in individual cases, the difference, however, must be regarded as uncertain. In the gastrectomy group the rise in the glycine concentration 2 hours after ingestion was greater than in any of the other groups. This is seen both from the mean values

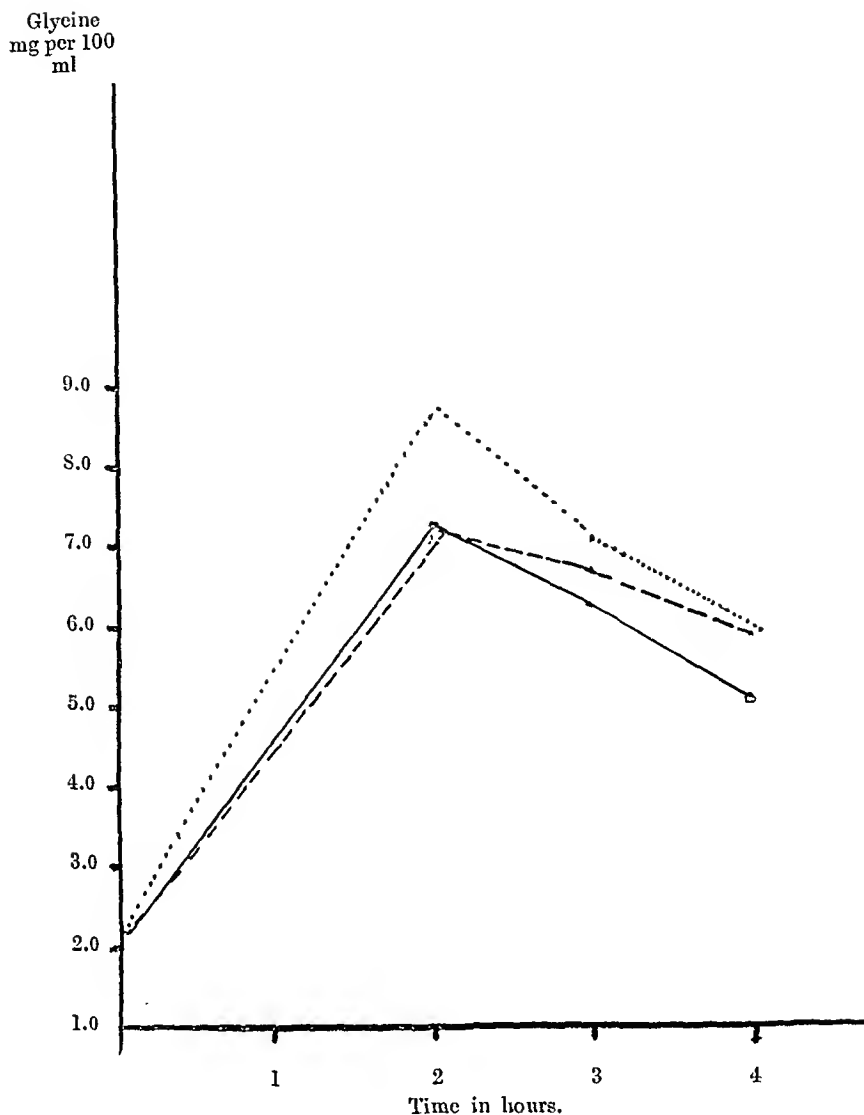


Fig. 4. Mean glycine values for the different test groups.

— Persons with achlorhydria.
 Persons with an earlier subtotal gastrectomy.
 - - - Persons with acid gastric secretion.

and the individual values which latter do not include as many relatively low curves as seen in the other groups.

In evaluating these results it should be noted that the tests were made with protein dissolved in water, which is emptied from the stomach more rapidly than solid protein. Different results may perhaps be obtained after the ingestion of meat in solid pieces, for instance.

Under the test conditions used, the results obtained indicate no difference in the

rate of protein digestion and absorption in persons with acid gastric secretion and those with achlorhydria. On the other hand, protein digestion is apparently somewhat more rapid in persons who have had a subtotal gastrectomy. The probable cause of this difference is the higher gastric emptying rate in these persons, which brings the ingested gelatine more quickly under the trypsin digestion. Following on this interpretation the results obtained are against the concept still held by many that the gastric emptying rate is increased in achlorhydria, since, if this were true, an abnormal rise in the glycine level could have been expected also in the persons with achlorhydria. The fallacy of this old theory of the rapid emptying rate in achlorhydria has already been proved by, for instance, the earlier investigations of one of the present authors (Brummer and Bundul).

Summary.

The authors have observed the rise in the plasma glycine level after the ingestion of gelatine. No difference was found between persons with achlorhydria and those with acid gastric secretion. On the other hand, in persons with an earlier subtotal gastrectomy the rise in the glycine concentration was apparently somewhat greater than in the other groups. The authors are of the opinion that this probably is a result of the more rapid gastric emptying rate in these persons.

References.

1. Alexander, B., Landwehr, G. and Seligman, A. M.: *J. Biol. Chem.* 160: 51, 1945. —
 2. Brummer, P. and Bundul, A.: *Acta med. Scand.* 140: 464, 1951. — 3. Brummer, P. and Ruikka, I.: *Ann. Med. int. Fenn.* 39: 81, 1950. — 4. Christensen, H. N. and Schwachman, H.: *J. Clin. Invest.* 28: 318, 1949. — 5. Everson, T. C.: *Surgery* 31: 511, 1952. —
 6. Farris, J. M., Ransom, H. K. and Coller, F. A.: *Surgery* 13: 823, 1943. — 7. MacDonald, R. M., Ingelfinger, R. J. and Belding, H. W.: *New Engl. J. Med.* 237: 887, 1947. — 8. Tomoda, M.: *Chirurg* 23: 545, 1952.
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The Mechanism of General Haemodynamic Changes in Heart Failure.¹

By

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(Submitted for publication June 25, 1953.)

Higher organisms exist in the ever-changing external environment thanks to the continuous equilibrating function of the central nervous system. Through a permanent out-flow of impulses to all organs and structures in the body, all the activities of the body undergo continuous modification. The functions of the body depend on an adequate supply of energetics and also on an adequate elimination of all the wastes. It is, therefore, natural that the circulatory system must be continuously adapted to ever changing requirements. It is therefore controlled either directly or indirectly — through the intermediary of humoral agents — by the leading influences of the central nervous system. The central nervous system is at the same time continuously informed about the conditions of the blood supply of the various parts of the body through nervous endings (intero-receptors) situated not only in the well-known locations such as the aortic and carotid sinus bodies but distributed throughout the whole cardiovascular system (Bykov (4), Čarnýj, Krasovickaja, Lantěva and Plutěnko (5), Peterson (22)) which are the starting points of vaso-motor reflexes.

When the diseased heart starts to fail, the ability of the cardiovascular system to respond adequately to the requirements of the body decreases. It may be supposed that the changed blood supply and, in consequence, the changed metabolism of the inadequately supplied regions, is the starting point of new impulses and, thus, of new reflexes altering the whole cardiovascular system. It seems likely that at the same time these impulses alter the whole reactivity and function of the organism which is gradually adapting itself to the new conditions created by heart failure. A new steady-state develops. It was found by others (7, 16) and by ourselves (3, 8) that heart-failure is characterized not only by a

¹ A preliminary report of these results was presented at the 1st International Congress of Cardiology in Paris in 1950 (published in the *Comptes Rendus* of this congress).

diminished performance of the diseased heart but also by an altered function of the whole cardiovascular system. The tendency to a fall in blood pressure due to the diminished cardiac output is counteracted by peripheral vasoconstriction. This differs in degree in various parts of the body changing thus the distribution of blood to various organs. A regular finding in congestive heart failure is a rise in venous pressure, explained by the majority of authors as a passive congestion behind the failing right ventricle. There are, however, several indications that veins are not passive tubes. Already Starling (26) suggested that active venoconstriction might occur in heart failure. This is also postulated on indirect grounds in asphyxiated dogs by Starr, Jeffers and Meade (27) who also found that a gross damage to the right ventricular muscle does not cause *per se* a passive elevation of the venous pressure. That veins have an active tone was pointed out already by Plesch (23). Evidence in favour of this statement can be found in everyday clinical practice *e. g.* in the disappearance of veins when touched by an injection needle. An active venous spasm prevents at times an easy introduction of the cardiac catheter and can be relieved almost instantaneously by an instillation of a few drops of a 1 % Procaine solution through the catheter. That an active elevation of the venous tone might be the cause of the increased venous pressure in heart failure seems to follow from the observations of Relman and Epstein (24), Hayward (12) and Halmágyi, Felkai, Iványi and Hetényi (11), who succeeded in reducing venous pressure in heart failure by TEAC or TEAB.

The mechanism through which the tone of the arterial and possibly of the venous part of the vascular bed is increased in heart failure and through which a new equilibrium is attained, has not yet to our knowledge been systematically investigated. From what has been said at the beginning, it seems that the changes must be mediated by the central nervous system. It can be, of course, questioned whether these supposed nervous influences affect the cardiovascular bed directly or through the intermediacy of some endocrine glands. Besides, some regulatory humoral mechanisms might be brought into action through direct changes of the blood supply or of the metabolism of various organs.

We tried to find an answer to the question which of these changes develop as a direct consequence of nervous influences by eliminating nervous adrenergic impulses affecting the blood vessels by Dibenamine (N,N dibenzyl- β -chloroethylamine). This substance is, according to Nickerson (20) the most specific adrenergic blocking agent and its probable effect is a competitive one: combining with the effector substance in the smooth muscles of the vascular wall, it prevents Epinephrine (Nor-adrenaline?) and Sympathin E from entering into combination with this substance. Dibenamine does not interfere with the liberation of Epinephrine from the adrenals and does not prevent Epinephrine from exerting its action on the striated heart muscle. It has a slight and inconstant side effect on the central nervous system. However, its peripheral effect does not seem to be mediated by the central nervous changes, the reaction to acetyl-choline, histamine, morphine, ergotamine, angiotonine and pitressin not being modified by Dibenamine.

Methods.

The investigation was carried out in 22 subjects, 5 of which were healthy, 2 were compensated cardiacs with mitral stenosis and 15 (8 males and 7 females) were cardiacs in failure of a various degree and severity. Their diagnoses are obvious from table 1. All subjects were kept in bed for several days prior to the investigation, they were on a normal ward diet and they were not treated by any cardiotonics or diuretics. On the day of the investigation they had a breakfast consisting of 250 ml of fruit juice and 1 biscuit and jam. The investigation started 6 hours after this breakfast and lasted for 4 to 8 hours. During the course of the investigation the subjects were kept recumbent and except for a small sip of fluid, they had nothing to eat or to drink.

The details of the experimental procedure were described in a previous paper (3). The investigation started about 1 hour after the introduction of the cardiac catheter, when the initial apprehension of most of the subjects disappeared and gave way to relaxation. During the following 90 to 120 minutes the blood pressure, pulse rate, respiration rate, respiration volume, vital capacity, oxygen consumption, cardiac output, arterial and mixed venous blood oxygen content and right auricular pressure were measured. When a satisfactory check of the successive values of the blood pressure and pulse rate was obtained, Dibenamine was administered in an intravenous drip. The dose varied between 3 to 10 mg per kg b. w. dissolved in 100 ml saline. The infusion was allowed to run for 29 to 64 minutes. All the estimated values were followed closely during the time of the infusion and for 1 to 4 hours afterwards. In 1 subject Dibenamine was substituted by 1 ml of Dihydroergotamine Sandoz i. v. This substance is thought to be an efficient adrenergic blocking agent. However, it is less specific than Dibenamine and much of its action is mediated by the central nervous system. Besides its action is of short duration, whilst that of Dibenamine develops gradually and lasts up to 24 hours. Blood-pressure was measured by a mercury manometer and by the auscultatory method of Korotkov. Respiration rate, respiratory volume per minute and vital capacity were estimated by Krogh's metabolimeter (no correction was made for the absorbed expired CO_2). Right auricular pressure was estimated by a water manometer attached to the cardiac catheter. Circulating plasma volume was estimated with Evans' blue using the extrapolation technique of Gregersen and Stewart (10). The circulating blood volume was calculated from this value, the relative proportions of plasma and red blood cells having been estimated by Wintrobe's haematocrit spun at 3,000 revolutions per minute. From the data the following values were calculated:

1) *Mean arterial pressure* was arbitrarily estimated as a mean of the systolic plus diastolic pressure.

2) *Peripheral vascular resistance* was expressed in dynes and was calculated from the following formula:

$$\text{Periph. resist.} = \frac{\text{Mean arterial pressure} \times 1,332}{\frac{\text{Cardiac output}}{60}}. \text{ Its normal values lie between 1,000}$$

and 1,400 dynes cm^{-5} sec.

3) *Oxygen utilisation* was calculated as oxygen consumption expressed as percent of the oxygen load $\left(\frac{\text{O}_2 \text{ consumption/1 min.}}{\text{O}_2 \text{ load/1 min.}} \times 100 \right)$. The oxygen load was calculated as the product of the cardiac output and the arterial oxygen content

$$\left(\frac{\text{Card. output ml} \times \text{Art. O}_2}{100} \right).$$

Its average normal values are 15–20 %.

4) *Respiratory volume per minute* is the product of respiratory volume and respiration rate per minute. It amounts normally to 8 to 10 liters.

5) *Harrison's ventilation index* is the ratio of the respiratory volume per minute and vital capacity. Our normal values are 1.2–4.2 with an average of 2.95.

6) *Ventilation equivalent* expresses how many liters of oxygen have to be breathed in to provide 100 ml of oxygen to the organism $\left(\frac{\text{respiratory volume/l min.}}{10 \times \text{oxygen consumption}} \right)$. Its normal values range from 3 to 5.

At the same time a detailed study of renal functions was carried out. The details of this investigation are presented in a subsequent paper.

Results.

According to Nickerson (20) miosis is the first sign of Dibenamine action in man. This sign was observed without exception in all our subjects who received Dibenamine and it appeared 16 to 122 minutes after the start of the Dibenamine infusion. 8 subjects complained of a feeling of dryness in the mouth appearing in one instance already 12 minutes after the start of the Dibenamine infusion. Other subjects experienced nausea and vomited some 1–3 hours after Dibenamine. Mental changes resembling light alcohol intoxication, change of mood with occasional visual hallucinations appeared in 8 subjects. In 2 subjects there was a marked mental depression and in one heavy drinker mental changes resembling delirium tremens appeared. All of these changes subsided within 2 to 3 hours after the start of the infusion. Mental changes and vomiting occurred in all 4 subjects who received the highest dose of Dibenamine, *i. e.* 10 mg per kg b. w. They were slight or absent in those subjects who received 5 mg or less Dibenamine per kg b. w. No toxic changes appeared in the subject who received Dihydroergotamine.

It may be stated already here that the haemodynamic changes which will be described forthwith and which appeared with a great regularity in all of the investigated subjects were independent of the toxic phenomena described above.

All the data of changes occurring after Dibenamine or Dihydroergotamine are computed in table 1, the first value being always the average of at least two control measurements prior to the administration of the adrenergic blocking agent. The results of 2 typical experiments, one in a normal subject and one in a severely decompensated cardiac are presented in fig. 1 and 2.

Subject M. P. (No. 2) was a 35 years old female, convalescent from an attack of pyelitis with normal urinary findings and normal renal function at the time of the investigation. Repeated estimations of the cardiac output, pulse rate, blood pressure and right auricular pressure before the start of the Dibenamine infusion gave approximately the same result. The infusion of 500 mg Dibenamine (10 mg per kg b. w.) was started some 150 minutes after the beginning of the first control measurement and the infusion ran for 70 minutes. Immediately after the end of the infusion cardiac output increased from its pre-infusion level of 6.65 liters to 8.94 liters, whereupon it started to drop and towards the end of the experiment some 4 hours after the beginning of the infusion it attained a low level of 2.94 liters per minute. These changes of the cardiac output were due to alterations of the stroke volume. This is clearly born out by the fact that there was a steady drop of the pulse rate during the infusion of Dibenamine, whereupon the pulse rate increased from 72 to 120–135 per minute and remained approximately at

the same level during the whole rest of the observation whilst the cardiac output was diminishing to about 1/3 of its highest level. The blood pressure started to decrease already some 30 to 40 minutes after the start of the Dibenamine infusion. Towards its end it attained the value of 90/60 mm Hg, later it increased again towards its initial level (105/70). It is obvious from fig. 1 that the peak of the cardiac output coincided with the lowest levels of the blood pressure. This points to a reduction of the peripheral vascular resistance which decreased from a control level of 1,078 dynes to 685 dynes. During the later stage of the observation when the cardiac output fell and blood pressure increased, there was a marked rise of the peripheral vascular resistance attaining towards the end of the observation 2,265 dynes. The changes of the right auricular pressure were very small and probably insignificant oscillating between $+1.7$ cm H_2O towards the end of the infusion of Dibenamine and -1.5 cm H_2O some 60 minutes later whilst the control pre-infusion figures averaged -0.5 cm H_2O .

Analogous changes were found in another normal subject M. B. (No. 1). Subject B. M. (No. 3), O. Z. (No. 4) and O. S. (No. 5) exhibited anxiety in the course of the whole observation. They were tense, the two latter had wide pupils and the blood pressure and right auricular pressure were at the upper limit of the normal level or slightly above it. Dibenamine depressed both these values towards normality. There was an increase of the cardiac output in subject B. M. and O. S. whilst the cardiac output in subject O. Z. exhibited only a dubious change. The fall in blood pressure with an unchanged or increased cardiac output is again an expression of a diminished peripheral resistance.

The course of the experimental observations in subject B. D. (No. 18), a 56 years old female suffering from a rheumatic heart disease with mitral stenosis, auricular fibrillation, marked congestive heart failure, with a relative tricuspid incompetence, is presented in fig. 2. Her cardiac output averaged 2.25 liters per minute. Like in the normal subjects, a tendency towards a rise of the cardiac output was noted towards the end of the Dibenamine infusion which was allowed to run for 62 minutes. The rise continued until the 110th minute when the cardiac output reached 4.2 liters. One hour later a gradual decrease towards 3.4 liters was observed. There was also a transient increase of the pulse rate. Like in normal subjects the peak of the pulse rate did not coincide with the peak of the cardiac output; also here, therefore, the increase of the cardiac output was due to an increase in the stroke volume. The initial values of the blood pressure were low (95/60 mm Hg). Under the influence of the adrenergic blocking agent they decreased very insignificantly to 85/55 mm Hg. The combination of an increased cardiac output with an almost unchanged blood pressure points again to a diminished peripheral resistance: it fell from 2,700 dynes to 1,370 dynes at the time of the highest increase of the cardiac output, rising towards 1,870 dynes in the second half of the observation. Changes of the right auricular pressure were observed as early as 20 minutes after the start of the Dibenamine infusion. 2 hours after its beginning, right auricular pressure fell from the initial value of 25 cm H_2O to 16 cm H_2O .

The results in the remaining subjects with heart disease are analogous. The only exceptional findings are in subject T. D. (No. 21) in whom there was neither acceleration of the pulse rate nor any increase in the cardiac output, although her peripheral resistance and right auricular pressure fell in the usual way. In subjects E. Ch. (No. 11) and J. K. (No. 12) there was a slowing instead of an acceleration of the pulse rate. In the one subject who received Dihydroergotamine (F. P., No. 8), cardiac output increased from 5.6 to 6.5 liters/minute. There was an acceleration of the pulse rate from 108 to 120 per minute and peripheral vascular resistance fell from 1,400 to 1,038 dynes. Changes of the right auricular pressure in this subject were irregular and rather insignificant.

The higher the original values of the right auricular pressure and of the peripheral vascular resistance, the greater was the extent of their reduction following Dibenamine (fig. 3 and 4). The slightly elevated values of the right auricular pressure

Table

Haemodynamic and respiratory changes after adrenergic blockade with Dibenamine or stages of

g = dosis of Dibenamine in mg and duration of the infusion; h = time after the onset of the in-
 output ml; l = Blood pressure mm Hg; m = mean arterial pressure mm Hg; n = peripheral vas-
 volume ml; r = Oxygen utilisation %; s = respiratory volume ml; t = respiration rate/l min.;
 equiva.

Case number	Initials	Age	Sex	Weight	Diagnosis	Dosis of Dibenamine in mg and duration of the infusion	Time after the onset of the infusion	Oxygen consump- tion ml/1 min.	A-V oxygen difference ml %	Cardiac output ml
a	b	c	d	e	f	g	h	i	j	k
1	M. B.	24	F	61	Normal	500 67'	20' 40' 115' 195' 260'	209 — 212.5 221.6 212.5 212.5	2.90 — 1.85 2.51 3.61 2.86	7,210 — 11,500 8,800 5,890 7,440
2	M. P.	35	F	50	Normal	500 70'	— 20' 40' 80' 115' 185' 245'	199 — — 278 222 213.5 200	2.99 — — 3.11 3.15 5.40 6.80	6,655 — — 8,910 7,050 3,960 2,940
3	B. M.	35	M	70	Normal	300 36'	— — 16' 65' 120'	190 199 307 235 308?	2.15 3.15 3.74 2.14 2.90	8,837 6,317 8,208 10,981 10,641
4	O. Z.	20	F	73	Normal	350 59'	— — 20' 37' 67'	291 302 — 255 256	3.48 3.48 — 3.63 3.18	8,340 8,680 — 7,020 8,050
5	O. S.	23	F	59	Normal	300 46'	— — 20' 35' 80'	175 194 — 218 189	2.93 2.84 — 2.67 3.34	6,025 6,830 — 8,160 5,660
6	F. V.	42	M	55	R. H. D.; M. S. Comp.	250 52'	— — 20' 52' 92'	248 287 — 244 288	6.25 5.73 — 6.15 4.67	3,990 5,010 — 3,970 6,170
7	A. G.	39	M	65	R. H. D.; M. S.; A. R.; Fibril.; Comp.	250 47'	— — 12' 49' 94'	343.7 345 340 392 371	2.98 2.97 4.02 2.25 2.70	11,586 11,610 8,460 17,400 13,750

1.

Dihydroergotamine (DHE 45) in normal subjects and subjects with heart disease at various heart failure.

fusion; i = Oxygen consumption ml/ 1 min.; j = A—V oxygen difference ml %; k = Cardiac eular resistance; o = right auricular pressure cm H₂O; p = pulse rate/1 min.; q = circulating blood u = respiratory volume per minute; v = vital capacity ml; w = Harrison's index; x = Ventilation lent.

Blood pressure mm Hg	Mean arterial pressure mm Hg	Peripheral vascular resistance	Right auricular pressure cm H ₂ O	Pulse rate/1 min.	Oxygen utilisation %	Respiratory volume ml	Respiration rate/1 min.	Respiratory volume per minute	Vital capacity ml	Harrison's index	Ventilation equivalent	Circulating blood volume ml
l	m	n	o	p	r	s	t	u	v	w	x	q
115/70	92	1,037	7.0	70	17.8	585	13	7,350	3,590	2.04	3.5	3,530
115/70	92	—	7.0	92	—	—	—	—	—	—	—	
110/70	90	626	7.0	94	11.3	600	15	9,000	3,550	2.53	4.23	
100/65	82	745	7.3	86	15.3	370	26	9,620	3,250	2.06	4.34	
98/60	79	1,055	7.5	75	21.9	400	24	9,600	3,400	2.82	4.51	
110/65	88	911	8.0	76	17.4	410	22	9,020	3,350	2.69	4.24	
106/75	90	1,078	— 0.4	88	20.3	390	20	7,800	2,025	3.87	3.91	3,350
106/75	90	—	+ 0.2	82	—	—	—	—	—	—	—	
100/75	87	—	0.0	80	—	—	—	—	—	—	—	
92/62	77	685	+ 0.6	—	22.2	400	20	8,000	2,280	3.51	2.87	
96/65	80	906	— 1.0	125	22.3	400	24	9,600	2,000	4.8	4.32	
102/70	86	1,700	— 1.0	120	37.0	370	20	7,400	2,500	2.06	3.46	
105/70	87	2,265	— 0.5	110	47.1	390	13	5,070	2,150	2.35	2.53	3,430
150/100	125	1,132	9.5	64	11.97	730	19	13,870	4,800	2.88	7.3	
125/90	107	1,296	8.5	64	16.8	870	17	14,790	5,050	2.92	7.33	
120/90	105	1,020	7.5	64	19.73	980	14	13,720	4,900	2.8	4.46	
120/85	102	745	3.0	86	11.69	850	15	12,750	5,050	2.52	5.41	
100/70	85	639	3.0	86	16.21	1,700	20	34,000	—	—	11.03	
130/100	115	1,120	6.7	68	21.0	860	12	10,770	2,915	3.52	3.57	2,840
145/72	108	973	4.5	80	19.9	670	18	12,060	2,550	4.73	3.99	
144/80	112	—	5.0	84	—	—	—	—	—	—	—	
144/85	114	1,315	4.2	76	21.2	660	17	11,220	2,350	4.77	4.4	
125/70	97	979	2.0	88	19.05	660	19	12,540	2,900	4.33	4.9	
150/108	129	1,675	3.3	80	19.2	430	28	12,165	2,475	4.92	7.0	2,620
190/85	138	1,597	3.0	122	17.97	480	38	18,240	2,150	8.48	9.4	
135/80	108	—	2.4	96	—	—	—	—	—	—	—	
125/80	102	1,007	2.0	100	17.24	490	30	14,700	2,350	6.25	6.74	
118/74	96	1,330	1.0	106	21.7	380	30	11,400	2,530	4.5	6.03	
120/80	100	1,925	5.5	90	33.3	685	19	13,380	3,800	4.5	5.34	3,680
110/76	93	1,510	6.5	130	30.4	830	19	15,770	3,200	4.93	5.5	
116/80	98	—	6.0	160	—	—	—	—	—	—	—	
118/76	92	2,020	7.0	180	32.6	870	21	18,260	—	—	7.5	
104/64	84	1,080	7.0	176	24.7	950	21	19,900	2,950	5.9	6.94	
115/67	91	677	11.0	98	15.31	803	18	14,620	—	—	—	3,900
130/85	108	736	12.5	96	15.26	750	20	15,000	3,070	4.8	4.23	
128/82	105	1,001	10.5	96	20.64	800	24	19,200	3,020	4.97	4.35	
116/78	97	442	8.0	127	11.49	1,000	28	28,000	3,000	6.4	5.65	
104/70	87	512	7.5	126	13.66	750	28	18,750	3,100	8.75	7.14	
										6.05	6.94	

Caso number	Initials	Ago	Sex	Weight	Diagnosis	Dosis of Dibonamine in mg and duration of the infusion	Time after the onset of the infusion	Oxygen consumption ml/1 min.	A-V oxygen difference ml %	Cardiac output ml
a	b	c	d	e	f	g	h	i	j	k
8	F. P.	51	M	59	Emphysema pulm. Cor pulm. R. F. ±	DHE 45'	— 20' 40' 112'	274.5 — 293.5 307	4.42 — 3.93 3.62	6,399 — 7,540 8,480
9	J. B.	58	M	71	Endomesaort. Lu.; I. H. D.; L. F. ±	350 68'	— 20' 40' 55' 105' 186' 255'	293 — — 320.5 307 289 289	4.81 — — 4.03 4.04 3.93 4.32	6,100 — — 7,930 7,590 7,350 6,700
10	J. K.	40	M		Auricular septal defect R. H. D.: M. I.; R. F. +		— — 17' 68' 89'	268 263 303 297 285.5	4.62 4.67 3.86 4.30 4.56	5,800 5,630 7,840 6,910 6,260
11	E. Ch.	66	M	66	Endomesaort. Lu. I. H. D. R. F. ++	350 59'	— 20' 40' 88'	332 — 293 262	6.63 — 4.58 3.41	5,065 — 6,400 7,680
12	J. K.	48	M	56	R. H. D.; M. S.; R. F. ++	300 52'	— — 20' 40' 80'	237 279 — 243 247	17.12 17.0 — 14.31 16.38	1,388 1,600 — 1,693 1,510
13	J. Š.	59	M	103	I. and H. H. D.; R. F. ++	500 54'	— 20' 40' 55' 92'	372 417 — 398 440	7.07 6.6 — 4.1 4.35	5,320 6,320 — 9,720 10,100
14	J. B.	48	F	71	R. H. D.; M. S. Ao. R.; R. F. ++ Fibril.	350 63'	— — 20' 50' 125'	252 254 — 179.5 264	14.7 10.3 — 9.18 8.93	1,715 2,470 — 1,955 2,960
15	M. P.	70	F	49	I. H. D.; R. F. ++	500 68'	— 20' 40' 64' 127' 205' 265' 368'	186 — — 171 182 167 153.5 153	7.10 — — 4.24 5.02 5.77 6.38 4.68	2,615 — — 4,039 3,620 2,890 2,410 3,270
16	M. H.	67	F	47	I. H. D.; L. and R. F. ++	500 82'	— 20' 40'	206.5 — —	6.0 — —	3,445 — —

Blood pressure mm Hg	Mean arterial pressure mm Hg	Peripheral vascular resistance	Right auricular pressure cm H ₂ O	Pulse rate/l min.	Oxygen utilisation %	Respiratory volume ml	Respiration rate/l min.	Respiratory volume per minute	Vital capacity ml	Harrison's index	Ventilation equivalent	Circulating blood volume ml
l	m	n	o	p	r	s	t	u	v	w	x	y
120/85	102	1,428	2.5	106	20.0	395	27	10,435	875	11.9	3.8	4,320
115/86	100	—	3.0	120	—	—	—	—	—	—	—	
120/92	106	1,130	3.0	108	17.75	400	22	8,800	850	10.35	2.94	
125/95	110	1,038	3.0	116	16.23	420	24	10,080	800	12.6	3.3	
200/40	120	1,595	6.5	82	35.6	460	23	10,590	2,750	3.85	3.6	4,170
195/30	112	—	7.0	82	—	—	—	—	—	—	—	
195/40	117	—	9.5	88	—	—	—	—	—	—	—	
200/40	120	1,214	5.4	88	31.9	450	30	13,500	2,200	6.13	4.21	
180/40	110	1,146	4.5	80	33.2	400	30	12,000	2,800	4.28	3.9	4,170
155/40	98	1,072	3.5	80	31.1	430	26	11,180	3,050	3.66	3.86	
152/35	94	1,120	3.0	86	34.5	490	24	11,760	2,900	4.05	4.07	
185/120	152	2,020	6.5	112	26.65	300	31	9,300	1,300	7.15	3.47	
170/110	140	1,980	6.0	100	26.7	270	38	10,260	1,050	9.76	3.90	4,170
150/100	125	1,260	6.5	108	23.6	300	31	9,300	1,130	8.23	3.06	
120/80	100	1,150	5.0	108	26.4	260	37	9,620	900	10.68	3.23	
120/80	100	1,264	4.3	100	28.5	350	33	11,550	1,070	10.79	4.04	
186/60	123	2,147	22.5	104	45.3	430	32	13,800	845	16.3	4.2	3,695
190/70	130	—	20.0	96	—	—	—	—	—	—	—	
185/90	137	1,560	15.5	92	33.2	430	27	11,610	750	15.5	3.96	
190/60	125	1,264	14.51	100	24.6	410	28	11,480	880	13.02	4.38	
160/120	140	7,850	12.0	120	80.9	375	28	10,500	1,500	7.46	4.16	3,620
155/105	130	6,390	11.5	130	79.7	420	44	18,500	1,700	10.87	6.62	
105/90	97.5	—	9.0	94	—	—	—	—	—	—	—	
120/90	105	4,930	9.2	82	66.75	370	40	14,800	1,650	8.97	6.1	
126/83	105	5,600	10.0	120	76.0	350	40	14,000	1,680	8.34	5.67	4,340
200/125	162	2,440	20.0	88	36.8	625	16	9,980	1,800	5.66	2.68	
200/110	155	1,978	21.0	92	33.7	500	20	10,000	1,900	5.26	2.39	
200/110	155	—	19.0	88	—	—	—	—	—	—	—	
200/110	155	—	19.5	98	—	—	—	—	—	—	—	4,270
206/114	160	1,305	17.5	106	22.3	540	21	11,340	1,700	6.67	2.84	
206/114	160	1,265	16.0	120	23.6	500	21	10,500	2,100	5.0	2.38	
130/110	120	5,320	32.5	140	70.9	320	36	11,520	500	2.3	4.57	
135/110	122	4,100	28.0	144	49.9	350	34	11,900	540	2.2	4.69	4,270
136/112	124	—	19.0	150	—	—	—	—	—	—	—	
133/110	122	4,990	18.0	152	44.14	390	33	12,870	500	2.58	7.17	
106/75	90	2,495	12.5	125	43.29	310	30	9,300	—	—	3.52	
140/80	110	3,265	7.0	64	36.5	300	22	6,740	1,450	4.65	3.62	3,890
140/80	110	—	6.0	66	—	—	—	—	—	—	—	
145/80	112	—	6.0	66	—	—	—	—	—	—	—	
144/80	112	2,145	6.0	72	23.13	300	23	6,900	1,080	6.38	4.03	
135/70	102	2,330	5.0	66	26.7	290	23	6,670	950	7.02	3.66	3,890
105/60	82	2,260	2.0	80	30.5	250	26	6,500	1,200	5.41	3.89	
112/64	88	2,925	1.4	80	35.9	260	22	5,720	1,050	5.44	3.72	
115/60	88	2,180	1.7	80	28.8	210	30	6,300	1,150	5.47	4.14	
170/80	125	3,010	3.1	88	38.3	480	22	10,800	890	12.1	5.25	2,890
160/75	118	—	1.5	88	—	—	—	—	—	—	—	
155/78	117	—	—	90	—	—	—	—	—	—	—	

Case number	Initials	Age	Sex	Weight	Diagnosis	Dosis of Dibenamine in mg and duration of the infusion	Time after the onset of the infusion	Oxygen consump- tion ml/1 min.	A-V oxygen difference ml %	Cardiac output ml
a	b	c	d	e	f	g	h	i	j	k
17	R. K.	70	F		I. H. D. R. and L. F. ++ Fibril.		58' 100' 150' 190' 270' 300' 360'	225.5 — 208.5 244 244.5 174.5 209	5.63 — 5.62 3.98 4.83 5.28 5.73	4,000 — 4,150 6,130 5,070 3,310 3,550
18	B. D.	56	F	67	R. H. D.; M. S.; R. F. +++ Fibril.	300 62'	— 20' 45' 112' 172'	171.5 — 207.5 203.0 201.0 192.0	5.37 — 5.28 5.97 4.06 4.66	3,193 — 3,930 3,400 4,950 4,120
19	S. Š.	69	M	66	H. H. D. and I. H. D. R. F. +++	300 29'	— — 11' 45' 75'	279.5 313 338 373 347	10.13 9.66 10.3 4.41 4.01	2,757 3,240 3,280 8,450 8,650
20	M. P.	46	F	50	R. H. D.; M. S. and M. R., Tr. R.; R. F. +++	200 44'	— — 18' 62' 106'	187 191 178 199 191	6.64 5.89 5.91 5.50 5.64	2,918 3,243 3,012 3,618 3,386
21	T. D.	70	F	56	I. H. D.; R. F. +++	250 68'	— 20' 40' 112' 195'	172 182 180 185.2 180	4.96 4.13 3.91 4.0 4.52	3,470 4,435 — 4,600 4,630 3,950
22	A. K.	61	M	87	Cor. pulmon. R. F. ++++	400 63'	— 20' 40' 60'	284 — 375 —	7.47 — 4.14 4.27	3,805 — 9,000 —

in subject No. 4, of the peripheral vascular resistance in subject No. 5 and of both these functions in subject No. 3, which, as mentioned previously, were presumably due to emotion, fell after the administration of Dibenamine to normal values. Although the changes recorded in fig. 4 and 5 are similar, two differences between them may be noted: 1) Whilst there was a reduction of the peripheral vascular resistance in all subjects, including those whose peripheral vascular resistance was normal, a decrease of the right auricular pressure occurred only

Blood pressure mm Hg	Mean arterial pressure mm Hg	Peripheral vascular resistance	Right auricular pressure cm H ₂ O	Pulse rate/1 min.	Oxygen utilisation %	Respiratory volume ml	Respiration rate/1 min.	Respiratory volume per minute	Vital capacity ml	Harrison's index	Ventilation equivalent	Circulating blood volume ml
l	m	n	o	p	r	s	t	u	v	w	x	q
180/85	132	2,640	0.5	98	35.8	450	27	12,150	850	14.2	5.38	5,060
180/80	130	—	0.5	120	—	—	—	—	—	—	—	
134/70	102	753	0.5	120	32.5	310	28	8,680	800	10.8	4.16	
110/66	88	1,180	0.7	145	26.7	350	30	10,500	800	13.1	4.30	
125/70	97	1,550	2.5	125	32.4	310	28	8,680	600	14.4	3.55	
115/70	92	2,375	3.0	135	33.2	350	28	9,800	630	15.5	5.61	
105/70	87	—	3.0	135	37.0	290	30	8,700	750	11.6	4.16	
190/95	142	3,570	16.0	88	33.63	360	19	6,840	1,300	5.26	3.98	
205/110	157	3,220	12.5	80	33.06	310	22	6,820	1,220	5.5	3.28	
175/100	137	3,235	14.0	76	36.65	280	23	6,440	1,100	5.85	3.17	
155/80	117	1,900	9.5	88	26.02	280	27	7,760	1,050	7.39	3.86	4,030
105/60	82	1,600	8.0	74	30.65	270	27	7,290	1,200	6.07	3.79	
105/60	82	2,782	25.0	122	56.8	455	30	13,600	625	21.8	5.83	
85/70	77	—	21.5	108	—	—	—	—	—	—	—	
90/70	80	2,037	21.0	128	48.2	350	26	9,100	500	18.2	4.15	
88/58	73	1,370	17.5	112	31.4	350	30	10,500	550	19.1	4.61	
86/62	74	1,871	17.5	100	38.5	350	30	10,500	500	21.0	4.95	
245/160	203	5,915	25.0	100	59.4	625	30	18,750	1,075	16.97	6.65	
235/155	195	4,790	27.5	92	58.9	580	38	22,040	—	—	7.04	
250/190	220	5,170	26.0	100	63.6	570	40	22,800	—	—	6.74	
240/165	203	1,875	15.0	109	32.4	500	42	21,000	—	—	5.63	3,185
200/110	155	1,442	11.5	104	29.6	400	36	14,400	—	—	4.15	
150/70	110	3,195	23.0	46	43.14	425	27	11,450	1,350	8.5	6.143	
170/80	125	3,080	19.5	62	39.83	420	28	11,760	1,200	9.8	6.137	
150/75	112.5	3,025	19.0	64	38.88	400	29	11,600	1,150	10.1	6.517	
140/80	110	2,425	16.0	96	38.01	380	35	13,300	—	—	6.683	
130/70	100	2,355	12.0	88	39.11	320	35	11,200	—	—	5.863	
90/50	70	1,599	8.5	84	31.8	330	27	8,910	750	11.9	5.2	
115/65	90	1,480	6.5	80	24.9	300	27	8,215	710	11.55	4.5	
110/65	87	—	6.5	86	—	—	—	—	—	—	—	
115/65	90	1,562	6.0	90	25.1	300	27	8,100	700	11.57	4.5	3,185
86/52	69	1,218	5.0	90	25.5	310	28	8,680	750	11.57	4.7	
86/52	69	2,175	4.5	86	27.7	300	27	8,100	650	12.46	4.5	
165/115	140	2,979	26.0	78	40.8	300	47	14,100	1,700	8.31	4.98	
155/110	132	—	—	—	—	—	—	—	—	—	—	
175/120	147	1,300	19.5	90	25.6	260	42	10,930	1,250	8.75	2.91	
190/120	155	—	15.0	100	34.3	—	—	—	—	—	—	

in 17 instances; it did not fall in the first two normal subjects and it remained unchanged or rose slightly above its original value in 3 subjects with heart disease (No. 6, 8, 16). 2) The fall of the peripheral vascular resistance was transient and it started to increase again some two hours later. On the other hand the fall of the right auricular pressure continued throughout the whole duration of the observation in 7 of the 11 subjects where this biphasic response of the resistance was observed. It remained unchanged in two subjects and only in two subjects

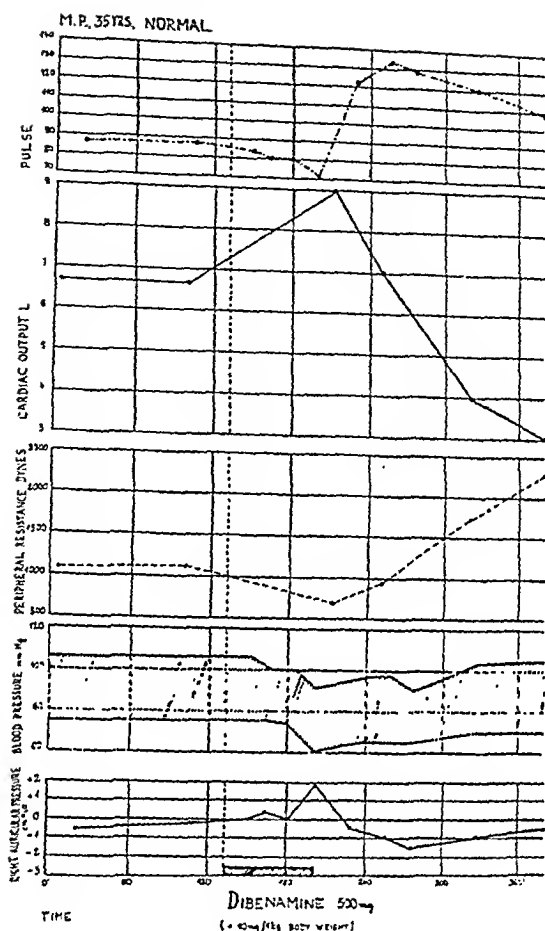


Fig. 1. Haemodynamic changes in a normal subject after Dibenamine.

a slight insignificant increase of the right auricular pressure was observed during this second phase.

There was an obvious correlation between the extent of the fall of the right auricular pressure or peripheral vascular resistance and their original values. No such correlation could be found between the original value of the cardiac output and its subsequent increase, nor could any relationship be noted between this transient increase of the cardiac output and the degree of the heart failure or dose of Dibenamine. The range of the transient increase of the cardiac output was between + 20 and + 313 % of its original value and the majority of the values lay between + 30 and + 90 %.

The first part of our observation may be summarized as follows: Following the adrenergic blocking agent there is a reduction of the increased right auricular pressure almost towards normal values in subjects with heart failure with a

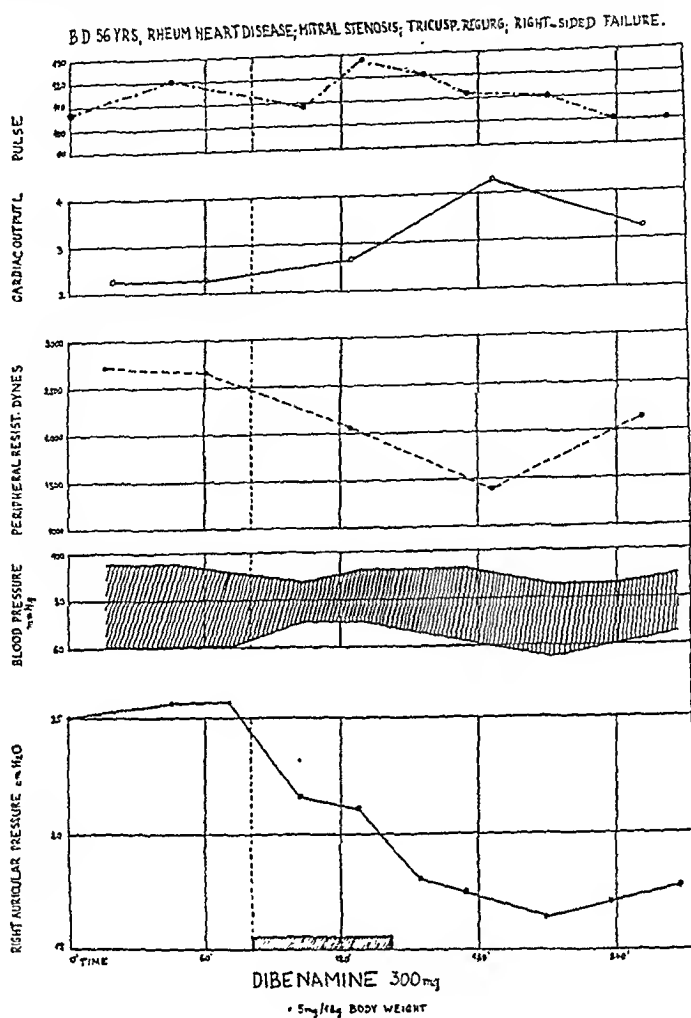


Fig. 2. Haemodynamic changes after Dibenamine in a subject with heart failure.

simultaneous transient reduction of the peripheral vascular resistance and an increase in cardiac output. In those subjects whose right auricular pressure was normal, Dibenamine did not produce any significant reduction of its value whilst it still reduced, though to a slight extent, peripheral vascular resistance and it increased the cardiac output even in normal subjects.

The next problem to answer is the time relationship of these changes and the question which of these changes are primary.

This answer will be difficult to find in observations which were not continuous. However, we may see from the data in the table and from fig. 1 that in 4 subjects (No. 1, 2, 8, 10) the cardiac output increased whilst the right auricular pressure remained unchanged. In subject M. P. (No. 15) whose right auricular pressure fell only very slightly from 7 to 6 cm H₂O, the cardiac output rose from 2.6 to 4.0 liters. In subject F. V. (No. 6), the increase in cardiac output was even accompanied by a slight rise from 5.5

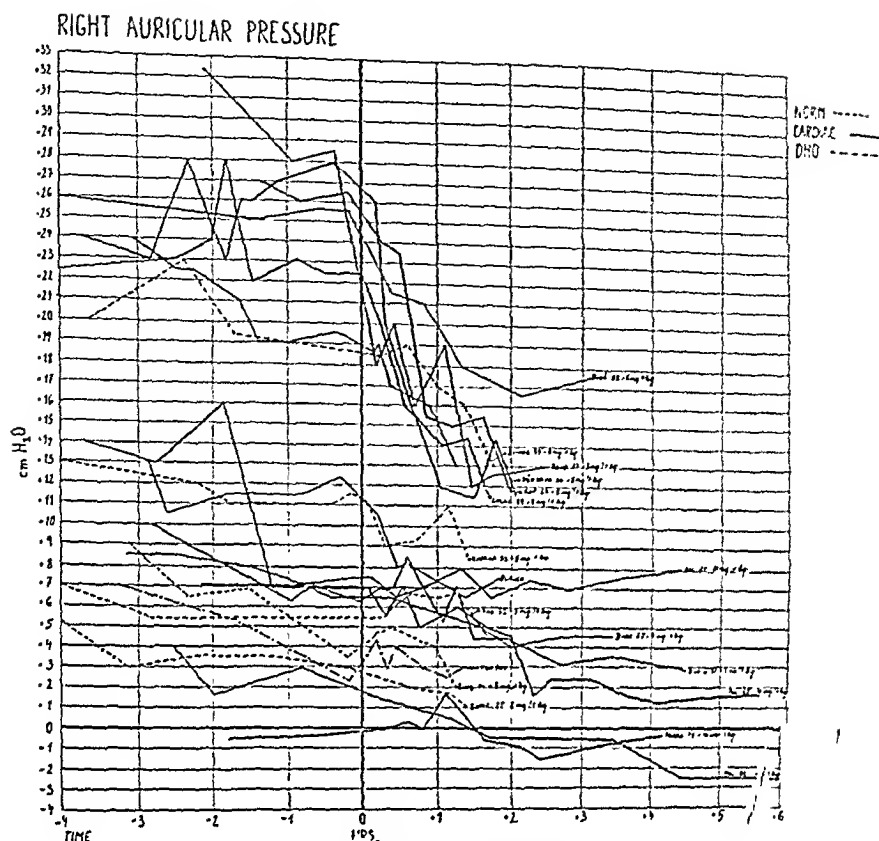


Fig. 3. Changes in the right auricular pressure after Dibenamine in normal subjects and in subjects with heart failure.

to 7.0 cm H₂O. On the other hand in subjects O. Z. (No. 4) and J. B. (No. 14), the fall of the right auricular pressure was accompanied by almost no change of the cardiac output and in subject A. G. (No. 7) was observed an early fall of the right auricular pressure which was accompanied by a decrease of the cardiac output. The later fall of the transiently increased cardiac output was never accompanied by any significant rise of the right auricular pressure as would be the case, should there be a reversed relationship between these two functions. On the contrary, in subjects No. 5, 9, 15, 16, 17 and 20, there was a further diminution of the right auricular pressure by 1 to 4 cm H₂O, during this secondary fall of the cardiac output.

Hence, we may conclude that there is no simple correlation between the changes of the right auricular pressure and of the cardiac output.

A far better correlation was found between the transient rise of the cardiac output and the fall of the peripheral vascular resistance. Although a few slight exceptions were noted to this general rule, the great majority of the data speak in favour of the conclusion that cardiac output and peripheral vascular resistance changed hand in hand.

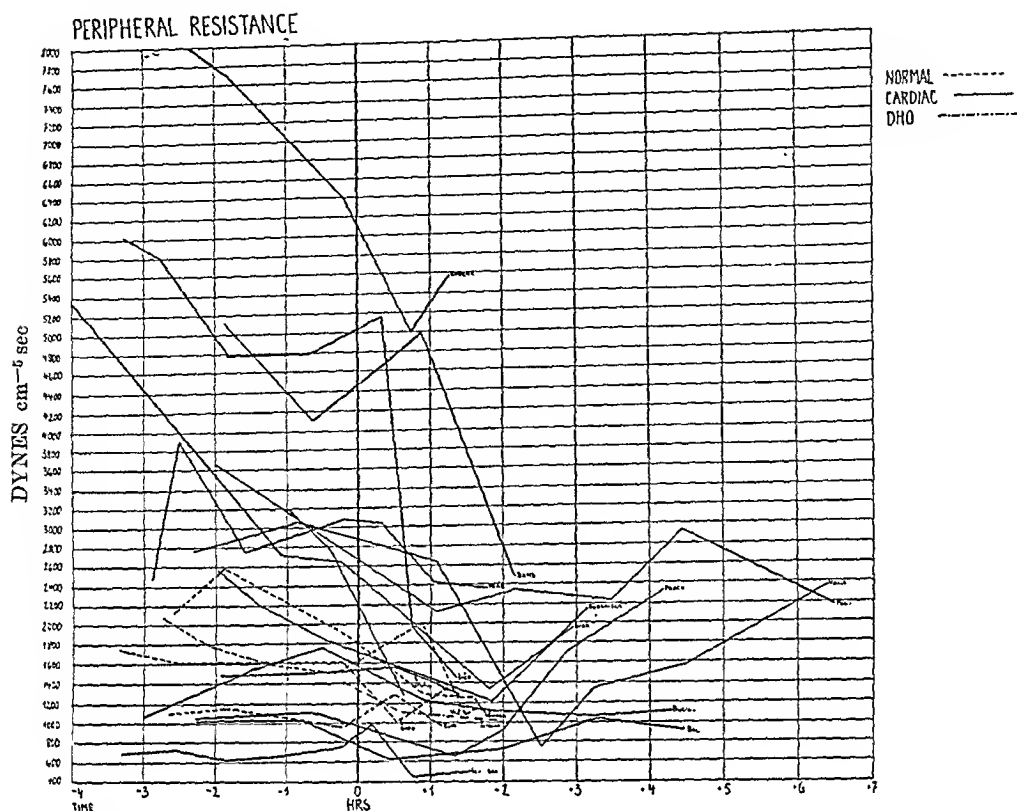


Fig. 4. Changes in peripheral vascular resistance after Dibenamine in normal subjects and in subjects with heart failure.

Three possible explanations for this relationship offer themselves:

1) The action of the adrenergic blocking agent on the cardiac output and on the peripheral vascular resistance was independent on each other.

2) The adrenergic blocking agent improved in some way the efficiency of the heart and the fall of the peripheral vascular resistance was secondary to this increased efficiency of the heart.

3) The adrenergic blocking agent diminishing the peripheral vascular resistance and consequently also the blood pressure brought into action secondary homeostatic mechanisms acting on the heart and counterbalancing by an increased cardiac output the fall of the peripheral vascular resistance.

The possibility of Dibenamine influencing directly the cardiac output seems to be very remote since Nickerson's demonstration that Dibenamine did not interfere with the Epinephrine stimulation of the heart in animals. On the other hand it is efficient in the prevention of the cardiac arrhythmias in Cyclopropane anaesthesia which points to some beneficial influence of Dibenamine on the heart. And since it was demonstrated by Gollwitzer-Meier (9) that the sympathetic has an adverse effect on the metabolism of the heart muscle, it seems necessary

to investigate the possibility of an improved metabolism of the myocardium as a consequence of the blockade of adrenergic stimuli.

We tried to find an answer to this question by examining the haemodynamic effect of bilateral anaesthesia of the stellate ganglia. Although it is certain that a part of the sympathetic fibers reaches the heart without passing these ganglia, they are, however, the cross road of the majority of the sympathetic fibers of the heart. Should Dibenamine increase the cardiac output by removing the adverse effect of the sympathetic impulses on the heart muscle, it was thought that blocking of the majority of the sympathetic fibers should produce at least a qualitatively similar effect to that of Dibenamine.

This investigation was carried out in 5 subjects. The anaesthesia of the stellate ganglion was performed with 5 to 10 ml of 1 % Cocaine solution (Cocaine was used instead of Procaine in order not to interfere with the determination of p-aminohippuric acid, used in the study of the renal plasma flow) by technique of Herget (13).

The anaesthesia was thought to be successful when the Claude Bernard-Horner syndrome appeared on both sides. In one subject (R. H.) the data were discarded because Cocaine penetrated quickly in the blood stream and produced central nervous symptoms resembling alcoholic intoxication. There were no adverse signs or symptoms in the remaining 4 subjects.

The results in one of the subjects are presented in fig. 5. It may be seen that there was an insignificant change of the cardiac output following the stellate ganglion anaesthesia and the blood pressure, peripheral vascular resistance and right auricular pressure remained virtually unchanged. The pulse rate which was steadily decreasing from the beginning of the observation, reached immediately after the stellate ganglion anaesthesia its lowest values. The changes produced by Dibenamine, administered 80 minutes later, were in sharp contrast with the effect of previous elimination of the sympathetic impulses reaching the heart and were similar to those previously described: the cardiac output and the pulse rate increased whilst peripheral vascular resistance diminished and there was a marked fall of the right auricular pressure.

Changes of the cardiac output, peripheral vascular resistance and right auricular pressure in the remaining 3 subjects were similarly insignificant.

These results seem to warrant the conclusion that the transient increase in the cardiac output after Dibenamine is not due to any interference with the nervous (sympathetic) impulses reaching the heart.

Thus the first two possible explanations for the increased cardiac output are refuted. The third possibility remains to be investigated. Several homeostatic mechanisms are brought into play when blood pressure starts to decrease. Out of these, renin, hypertensin and VEM are not known to increase the cardiac output and just the opposite, *i. e.* a fall of the cardiac output was described after the first two (Bradley and Parker (2)). The possibility that Epinephrine was the agent responsible for the transient increase of the cardiac output when peripheral resistance was diminished seems on the other hand to be the more probable one as it would explain at the same time the observed acceleration of the heart action. Two kinds of experiments were designed in order to examine this possibility. In 5 subjects haemodynamic effects of a hypodermic injection of 1 ml of a 1/1,000 solution of Epinephrine were compared with those of a subsequent infusion of Dibenamine, administered some 60 to 90 minutes later when all the changes

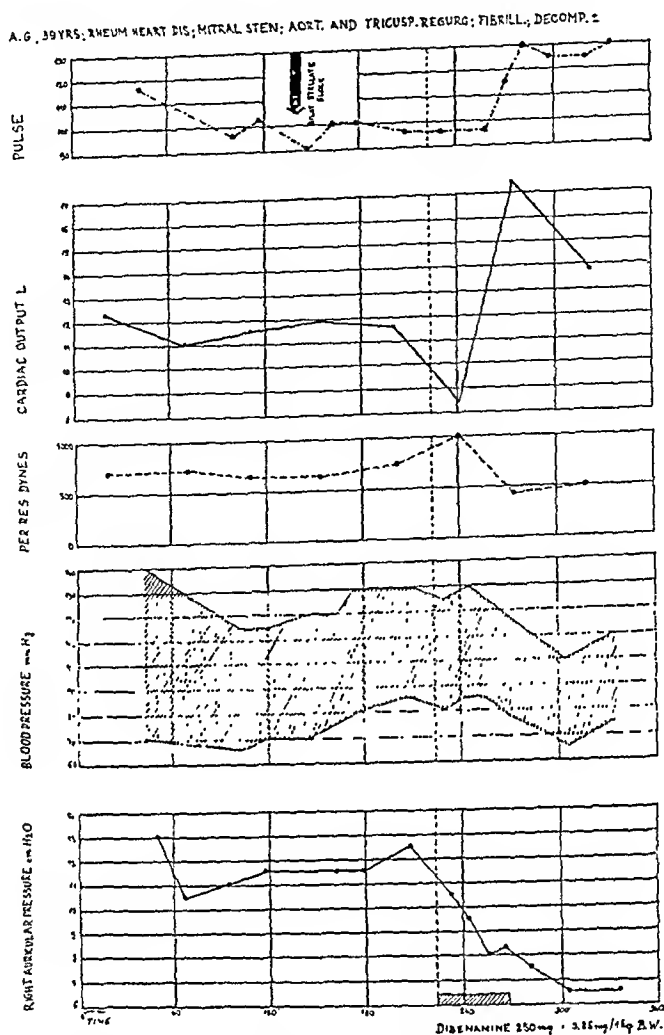


Fig. 5. The effect of bilateral blockade of the stellate ganglion and of Dibenamine on haemodynamics.

produced by Epinephrine disappeared, and with the effect of a further hypodermic injection of the same amount of Epinephrine given at the height of the Dibenamine action. In further 6 subjects the changes of blood sugar were followed before and after infusion of Dibenamine which according to Nickerson (20) does not interfere with the well known hyperglycaemic action of Epinephrine.

Results of the first series of investigations in which the action of Epinephrine was compared with that of Dibenamine, are presented in table 2. An increase of the cardiac output by 22.3 to 57.9 % of its original value was noted in all 5 subjects between 10 to 20 minutes following the injection of Epinephrine. This increase was due in the first place to an acceleration of the heart rate which occurred in all instances. The stroke volume, on the other hand, rose only twice, whilst it remained unchanged in one subject and fell in the remaining two subjects. Dibenamine produced only a minor change of the cardiac output in subject O. Z. (No. 4), whilst in the remaining subjects cardiac

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Changes of the cardiac output and of its components after A) Adrenaline

The first line gives control values, the second line indicates highest values after the administration of adrenaline

Number	Name	Age	Sex	Diagnosis	A. Adrenaline									
					a		b		c		d		e	
					C. O. ml		Pulse		Stroke vol.		O ₂ ml		A-V diff.	
					abs.	%	abs.	%	abs.	%	abs.	%	abs.	%
1	J. K.	48	M	R. H. D.; M. S. R. F. +	1,388		119		11.65		237		17.12	
					1,725	+ 24	150	+ 26	11.50	- 1.3	298	+ 25.6	17.27	+ 0.8
2	F. V.	42	M	R. H. D.; M. S. Comp.	3,990		92		43.10		248		6.25	
					5,080	+ 27.3	132	+ 43.5	38.50	- 11.3	300	+ 21.0	5.90	- 5.5
3	J. Š.	59	M	I. H. D.; H. H. D. R. F. ++	5,320		88		60.4		372		7.07	
					8,400	+ 57.9	92	+ 4.5	91.4	+ 51.2	420	+ 13.0	5.00	- 29.3
4	O. Z.	20	F	Normal.	8,340		69		120.8		291		3.18	
					10,200	+ 22.3	77	+ 11.5	132.2	+ 9.3	295	+ 1.3	2.89	- 17
5	O. S.	23	F	Normal.	6,025		82		73.5		175		2.93	
					8,340	+ 38.2	120	+ 46.0	69.4	- 5.6	217	+ 24.0	2.60	- 11.3

output increased by 22.3 to 82.7 % compared with the control values at the start of the observation and by 6 to 56 % compared with the values immediately prior to the administration of Dibenamine. This increase was brought about in 2 subjects solely by an increase in the pulse rate and in 2 by an increase in the stroke volume whilst in the remaining one both factors contributed to this increase. In subjects J. K. and O. S. in whom Epinephrine produced a rise of the cardiac output exclusively by an acceleration of the pulse rate, Dibenamine produced the increase in cardiac output through an augmentation of the stroke volume with a simultaneous slowing down of the pulse rate.

Epinephrine injected at the peak of the Dibenamine effect produced an increase in the cardiac output only in subjects J. Š. and O. S. In both, there was an increase of the stroke volume but only in subject O. S. an acceleration of the heart rate was noted. In the remaining 3 subjects a slight decrease of the cardiac output occurred.

The mechanism of the increase in cardiac output after Dibenamine differed qualitatively in 4 subjects from the mode of its increase after Epinephrine. Besides, in 3 out of the 5 subjects Epinephrine affected the cardiac output at the time of the full Dibenamine effect only insignificantly and in a rather inversed way. On the other hand, in 2 subjects the changes produced by Epinephrine at the peak of the Dibenamine effect were similar to those produced by pure Epinephrine and to a certain extent to the changes of the cardiac output produced by Dibenamine.

These observations are thus inconclusive. However, more reliable results were obtained if the changes of the cardiac output were compared with the changes of the oxygen consumption. It is a well established fact that Epinephrine increases the oxygen consumption in the body. Dibenamine does not interfere with the metabolic effects of Epinephrine. Should, therefore, the increase in cardiac output after Dibenamine be a secondary consequence of the mobilisation of Epinephrine, it should be accompanied by a concurrent increase in the oxygen consumption.

) Dibenamine and C) Adrenaline injected during the action of Dibenamine.

cedure. The left column contains absolute values, the right column indicates changes in per cental value.

Dibenamine								C. Dibenamine + Adrenaline										
b		c		d		e		a		b		c		d		e		
Pulse		Stroke vol.		O ₂ ml		A—V diff.		C. O. ml		Pulse		Stroke vol.		O ₂ ml		A—V diff.		
%	abs.	%	abs.	%	abs.	%	abs.	%	abs.	%	abs.	%	abs.	%	abs.	%	abs.	%
12		12.1		279		17.0		1,510		120		12.6		247		16.38		
30 — 39.4		21.2 + 75.3		243 — 12.9		14.31 — 16.4		1,373 — 9.0		146 + 21.8		9.4 — 25.5		225 — 8.9		16.41 + 0.2		
12		38.0		287		5.73		6,170		174		39.0		288		4.67		
4 + 31.8		39.0 + 2.5		288 ± 0		4.67 — 18.5		5,770 — 6.5		72 — 58.6		80.0 + 105		300 + 4.0		5.20 + 11.3		
12		67.7		417		6.60		10,100		120		84.2		440		4.35		
8 + 17.2		90.0 + 33.0		398 — 4.5		4.10 — 32.4		26,900 + 166.3		118 — 1.7		228 + 171		470 + 6.7		1.75 — 59.8		
30		108.3		291		3.48		8,050		88		91.6		256		3.18		
8 + 10.0		91.6 — 15.8		256 — 12.0		3.18 — 8.7		7,580 — 5.8		94 + 6.8		80.7 — 11.8		272 + 6.1		3.59 + 13.0		
12		61.0		194		2.84		5,660		108		52.4		189		3.34		
10 — 10.6		81.6 + 33.8		218 + 11.0		2.67 — 6.0		8,240 + 45.2		138 + 27.8		59.7 + 14.0		243 + 28.6		2.95 — 11.6		

In 4 out of the 5 subjects hypodermic injections of Epinephrine produced an increase in the oxygen consumption. Dibenamine had a similar effect only in 1 subject whilst in subject F. V. the oxygen consumption did not change and in the remaining 3 it decreased. In subjects F. V. and J. Š. the increase in cardiac output after Dibenamine was of the same degree as after Epinephrine. On the other hand, in subject O. S., in whom an increase in the oxygen consumption after Dibenamine was observed, the increase in cardiac output after Dibenamine was only half as great as after Epinephrine. The injection of Epinephrine at the peak of the Dibenamine action produced a significant increase of the oxygen consumption of 28.6 % in one subject, a rather insignificant increase of 4—7 % in three subjects and a fall of 9 % in the remaining one. In the two subjects in whom Epinephrine produced an increase in the cardiac output at the peak of the Dibenamine effect, an increase in the oxygen consumption was also noted. Dibenamine which caused an increase in the cardiac output of 56.3 % in the first of these two subjects, reduced insignificantly the oxygen consumption by 4.5 %.

These observations do not favour the idea that Epinephrine is the agent producing the increase in the cardiac output whilst peripheral resistance is low after Dibenamine. That this conclusion is correct was confirmed by the second series of the observations in which plasma glucose, estimated by the method of Somogyi (25) was followed throughout the observation. Results of these observations are presented in table 3.

The usual rise of the cardiac output was observed in subjects B. M., B. T., J. K. and R. K. In none of them was this increase in cardiac output accompanied by any significant change of the plasma glucose level. Subjects S. Š. and V. L. behaved rather surprisingly in that they were the only two in whom Dibenamine produced no increase in the cardiac output. In subject S. Š. an explanation for this different behaviour might be sought in the very high control values of the cardiac output due probably to anxiety. The

Table 3.

Changes of the haemodynamic functions and of blood sugar during sympathoadrenal blockade with Dibenamine.

a) number, b) initials, c) sex, d) age, e) diagnosis, f) time from the beginning of the Dibenamine infusion, g) pulse rate, h) cardiac output ml, i) blood pressure, j) peripheral vascular resistance (dynes), k) right auricular pressure cm H₂O, l) glycaemia.

Case number	Initials	Sex	Age	Diagnosis	Time from the beginning of the Dibenamine infusion	Pulse rate 1 min.	Cardiac output ml	Blood pressure	Peripheral vascular resistance dynes	Right auricular pressure cm H ₂ O	Blood sugar
a	b	c	d	e	f	g	h	i	j	k	l
1	B. M.	M	35	Normal	—	64	8,837	150/100	1,132	9.5	92
					—	64	6,317	125/90	1,296	8.5	89
					16'	64	8,208	120/90	1,020	7.5	84
					65'	86	10,981	120/85	745	3.0	80
					120'	86	10,641	100/70	639	3.0	95
2	S. Š.	M	24	Normal	—	120	21,250	—	—	2.0	110
					—	116	13,940	140/110	718	2.0	118
					17'	124	11,850	110/80	641	1.5	94
					62'	142	5,020	95/65	1,278	1.5	106
					112'	124	7,380	90/73	884	1.5	108
3	V. L.	M	42	Glomerulonephritis chron.	—	80	7,093	190/120	1,750	4.0	91
					—	80	6,005	185/120	2,015	4.3	92
					15'	100	5,853	160/110	1,840	3.0	92
					48'	104	4,703	130/80	1,774	3.5	106
					92'	100	3,625	105/75	1,985	2.5	112
4	B. T.	F	53	R. H. D.? M. S.? Comp.	—	84	9,390	135/110	1,042	4.5	102
					—	86	11,400	130/105	824	5.0	101
					17'	100	3,670	90/60	1,633	4.5	101
					60'	84	8,730	120/85	938	3.0	112
					92'	88	9,330	110/85	835	4.5	98
5	J. K.	M	40	Auricular septal defect; M. R., R. F. +	—	112	5,800	185/120	2,020	6.5	98
					—	100	5,630	170/110	1,950	6.0	104
					17'	108	7,840	150/100	1,260	6.5	104
					68'	108	6,910	120/80	1,150	5.0	104
					89'	100	6,260	120/80	1,261	4.3	104
6	R. K.	F	70	I. H. D. Fibril. L. F., R. F. ++	—	88	3,193	190/95	3,570	16.0	98
					—	80	3,930	205/110	3,220	12.5	96
					15'	76	3,400	175/100	3,235	14.0	98
					65'	88	4,950	155/80	1,900	9.5	92
					119'	74	4,120	105/60	1,600	8.0	97

accelerated pulse rate and increased blood pressure which was reduced by Dibenamine, speak in the same sense. In subject V. L. who was relaxed and perfectly calm throughout the course of the investigation, no obvious reason for this different behaviour was found. However, we are lacking investigations in further subjects with chronic glomerulonephritis and renal hypertension. In both these subjects there was an increase in pulse rate following Dibenamine of the same type as in the other subjects. However, this acceleration of the heart rate was not accompanied by any change of the plasma glucose concentration.

We may conclude, therefore, that Epinephrine was not the mediating agent through which the diminished peripheral vascular resistance influenced the cardiac output.

A consequence of the diminished cardiac output in heart failure and of the decreased oxygen load is an increase of the oxygen utilisation in the tissues. Due to this increased oxygen utilisation, the oxygen consumption reflecting the general tissue metabolism, remains unchanged in the majority of the cardiacs. In all our heart patients without exception the transient increase of the cardiac output following Dibenamine was connected with a fall of the arterio-venous oxygen difference and hence also of the oxygen utilisation. This behaviour demonstrates that the transient increase in the cardiac output is connected with an improvement of the total circulation. The oxygen consumption increased in 18 subjects during the temporary rise of the cardiac output. However, its increase is in almost all subjects of a lower order than the increase in the cardiac output.

It was surprising that the general improvement of the circulation during the transient increase in the cardiac output was neither connected with any significant or consistent changes in vital capacity, nor in the Harrison's index, although these two functions seem to be a very sensitive index of the degree of the cardiac decompensation. Moreover, changes of the Harrison's index did not parallel closely changes of the vital capacity. This was due to the fact that irregular variations of the respiratory volume per minute occurred in the course of our observations. In 17 subjects there was some increase in the respiratory volume per minute at some stage of the observations following Dibenamine. This increase was due in 5 subjects (No. 3, 5, 6, 10, 14) to a greater depth of the individual respirations. In the remaining subjects the predominant changes in the oxygen consumption after Dibenamine being small and that of the respiratory volume per minute being inconsistent, it follows that also the changes of the ventilation equivalent indicating how many liters of oxygen have to pass to the lungs per minute in order to supply the organism with 100 ml of oxygen (our normal figures range between 2.5 to 4.5 liters) were also inconsistent. No regularity was found even among subjects belonging to the same etiological subgroup.

Discussion.

The following points seem to be born out by our observations: blocking of adrenergic impulses diminishes the increased venous pressure in congestive heart failure and leaves the normal venous pressure of subjects without any evidence of heart failure unaffected. A similar effect on right auricular pressure was found in 3 subjects who had no evidence of organic heart disease but who — showing definite signs of marked anxiety — differed from all the other subjects who were fully relaxed throughout the course of the observation. This reduction of the pathologically high venous pressure in congestive heart failure occurred irrespective of any changes of the cardiac competency as judged by the cardiac output and of any changes on the arterial side of the vascular system. The degree of the reduction of the right auricular pressure was directly proportional to the degree of its original elevation. Although in those subjects who had the highest right auricular pressure even their lowest values following Dibenamine were still

above the normal range, we may conclude that the elevation of the venous and right auricular pressure in congestive heart failure was — at least to a great extent — of nervous (adrenergic) origin. Whether some other — possibly humoral — factors were also at play and partook in the elevation of the right auricular pressure, cannot be decided on the present evidence. It is possible that an overfilling of the venous vascular bed, as suggested by Warren and Stead (28) might be responsible for the residual elevation of the right auricular pressure after the adrenergic blockade. Also Halmágyi et al. (11) produced recent evidence that the elevated venous pressure after an overfilling of the venous vascular bed with saline behaved differently from the increased pressure in heart failure in that the first did not respond to TEAB whilst the other one did. Our findings are compatible with the idea that the residual elevation of the venous pressure after Dibenamine had some connection with an increased blood volume: Of the 12 subjects with a circulating blood volume above 3,500 ml per sq. m. body surface right auricular pressure remained outside the normal range after Dibenamine in 9, whilst of the 6 subjects with a circulating blood volume below 3,500 ml/sq. m. body surface only 2 had right auricular pressures higher than 5 cm H₂O following Dibenamine (see table 1). Our results also clearly demonstrate that blocking of the adrenergic impulses reduced peripheral vascular resistance and that this reduction was not secondary to any changes in cardiac competency. In analogy to the behaviour of the right auricular pressure also the fall of the peripheral vascular resistance was most marked in those subjects where its original values were highest. This again points to a nervous (adrenergic) mechanism underlying this abnormal increase in peripheral vascular resistance.

On the other hand the effect of the adrenergic blocking agent on cardiac output was secondary to changes in the peripheral vascular resistance. A superficial glance at some of our data, where cardiac output increased at the time when the increased venous pressure started to fall, might recall the suggestion of McMichael et al. (14) that the reduction of the cardiac output in heart failure was a consequence of the high venous pressure. This impression was, however, refuted by a thorough scrutiny of our results as pointed out previously. There was no correlation between the fall of the right auricular pressure and the transient increase in the cardiac output. Both components take part in the elevation of the cardiac output after Dibenamine: there is an elevation of the stroke volume and an acceleration of the heart rate. An exploration of the possible mechanisms through which a fall of the peripheral vascular resistance might increase the cardiac output excluded Epinephrine as the possible humoral agent. At present there is no other known humoral agent with the same effect on cardiac output which could be released during the period of hypotension. The remaining possibility is that the increase in cardiac output is due to a reflex. We must recall that nervous impulses reaching the heart are not blocked by Dibenamine. It was demonstrated by Warren and Stead (29) that a reduction of the peripheral vascular resistance produced by a release of constricting tourniquets on both thighs was followed by an immediate rise of the stroke volume. This immediate response following within a beat from the release of the tourniquets could not possibly

be mediated by any humoral agent and was certainly of a reflex nature. Aviado, Lu, Kalow, Peskin, Turnbull and Hess (1) recently produced evidence that an increase in pressure in the left ventricle brought forward a reflex bradycardia and a slowing down of the circulation. It may be imagined easily that opposite changes of the intraventricular pressure have an opposite effect on haemodynamics. A fall of the peripheral vascular resistance produced by Dibenamine was probably connected with a reduction of pressure in the left ventricle. In view of the experimental findings of Aviado et al. (1) reflex tachycardia and a reflex increase in cardiac output is to be expected under these circumstances. This also happened. It is, of course, difficult to localize with certainty the respective baroreceptors. The work of Bykov et al. (4) demonstrated, however, clearly that there are nervous endings (interoreceptors) throughout the whole vascular system.

It would be tempting to think that the secondary fall in cardiac output was due to a diminished venous pressure and thus to a diminished filling pressure of the heart. However, it seems unlikely, in view of our findings that the secondary fall in cardiac output was not accompanied by any further reduction of the venous pressure. On the other hand the peripheral vascular resistance increased during this later fall of the cardiac output. We are unable to say at this stage of our work what was the mechanism of this secondary increase of the peripheral vascular resistance but we may think of the activation of secondary homeostatic mechanisms like renin or VEM.

It was surprising that we did not find any improvement in vital capacity or Harrison's index during the phase of the transient increase in the cardiac output although the fall in the arterio-venous oxygen difference and in the oxygen utilisation pointed to an improvement of the circulation. The failure of these two functions to improve points rather to our inability to register momentary alterations of the pulmonary circulation.

Our findings indicate that when the heart starts to fail, there is no gradual passive decline of the efficiency of the circulation but that the whole vascular system is rebuilt by reflexes originating probably in interoreceptors of the whole vascular bed stimulated either by a decline in pressure or by some metabolic changes, which are so far undefined. Reflex arteriolar vasoconstriction prevents a fall in the general blood pressure. Being of irregular distribution it insures adequate blood supply to some of the vital structures but at the expense of some other organs whence blood is drawn away. One of these structures is the kidney (3, 8, 17, 18), the other possibly the skin (30). This reflex is probably an exaggeration of the normal reflex distribution of blood occurring whenever increased demands are thrown upon a fully efficient circulation such as under conditions of heavy physical work. Reflex increase of the venous tone, by diminishing the size of the venous vascular bed, contributes to an improved venous return of blood and may lead in the way suggested by McMichael (14) to a better diastolic filling of the heart and thus to its improved efficiency. However, the heart itself is also influenced from the periphery. This influence might be a mechanical one. It has to work under an increased filling pressure and against an increased peripheral vascular resistance. However, this increased resistance influences adversely

the competency of the heart also by a reflex mechanism. A vicious circle is thus closed: a failing heart activates reflex mechanisms building over the periphery and this in turn diminishes further the ability of the heart to perform its task. Moreover, a long-term active reflexly induced deprivation of various organs of an adequate blood supply interferes finally with their function and thus contributes to the disturbance of the whole organism. This theoretical conclusion lends support to the idea that in future it will be necessary to focus our therapeutic attention not only around the primarily diseased heart but also around the disturbed nervous regulation of the whole circulation.

Summary and Conclusions.

1. The mechanism of the genesis of the general haemodynamic changes in heart failure was studied by means of the neurohumoral adrenergic blockade induced by Dibenamine (and in 1 subject by Dihydroergotamine) in 17 subjects at different stages of heart failure and in 5 subjects with a normal cardiovascular system.
2. The earliest sign of the adrenergic blockade was a fall in the right auricular pressure, the extent of which was proportionate to its original elevation. Normal right auricular pressure was not affected by this blockade.
3. Peripheral vascular resistance decreased in all subjects. The extent of this decrease was also proportional to its original elevation. Its change was independent of the change in right auricular pressure. Also in normal subjects peripheral vascular resistance decreased by some 30 % of its original level. It follows that — contrary to the venous system — the nervous system contributes to the maintenance of the normal arteriolar tone. At later stages of our observations there was sometimes a new increase of the peripheral vascular resistance whilst the signs of a full adrenergic blockade were well maintained on the venous side. The secondary rise of the peripheral vascular resistance was probably due to the influence of secondary homeostatic mechanisms.
4. Cardiac output increased transiently in all subjects after the administration of Dibenamine. However, its increase was not proportionate to the extent of its original diminution nor to the extent of the changes in the right auricular pressure but its changes were always related to changes in peripheral vascular resistance.
5. In 5 subjects the effect of bilateral stellate ganglion anaesthesia was compared with the effect of Dibenamine administered some 2 hours later. Whilst the anaesthesia of the stellate ganglion had practically no effect on the cardiac output, peripheral vascular resistance or right auricular pressure, Dibenamine produced in all the subjects a fall in right auricular pressure whenever it was increased and in peripheral vascular resistance and a rise of the cardiac output. It was concluded that Dibenamine did not increase the cardiac output by blocking adrenergic impulses to the heart.

6. The effect of Dibenamine on cardiac output differed from the effect of 1 ml 1/1,000 sol. of Epinephrine administered hypodermically to 5 subjects. In 6 subjects the general haemodynamic changes brought about by Dibenamine were not accompanied by any changes of the blood sugar level. It was concluded that Epinephrine was not the mediator of the changes of the cardiac output during hypotension following Dibenamine infusion.

7. The transient increase in cardiac output was accompanied in all subjects with heart disease by a fall in the arterio-venous oxygen difference and in the utilisation of oxygen.

8. The increase in cardiac output was usually accompanied by an increase in oxygen consumption and vice versa. The changes of oxygen consumption were of a lesser degree than the changes in cardiac output.

9. Respiratory volume per minute varied in most instances in the same direction as oxygen consumption. The change was due mostly to a variation in the respiratory rate whilst the depth of respiration usually decreased.

10. Ventilation equivalent increased always when respiratory volume per minute increased and vice versa.

11. Vital capacity and Harrison's index did not exhibit significant or concordant changes and their minor fluctuations do not allow any conclusions as to the state of pulmonary haemodynamics following Dibenamine.

12. It was concluded that in heart failure interoreceptors of the whole vascular bed are the site of origin of new impulses which increase reflexly the arterial and venous tone and are the cause of numerous secondary effects.

References.

1. Ariado, D. M., T. H. Lu, W. Kalow, G. W. Peskin, G. L. Turnbull and M. E. Hess: *Am. J. Med. Sci.* 220, 707, 1950. — 2. Bradley, S. E. and B. Parker: *J. Clin. Invest.* 20, 715, 1941. — 3. Brod, J. and Z. Fejfar: *Quart. J. Med.* 19, 187, 1950. — 4. Bykov, K. M.: *Kora golovnogo mozga i vnutrennie organy*. Moskva 1947. — 5. Čarnyj, A. M., S. E. Krasovickaja, N. N. Lant'va and A. E. Plutěnko: *Klin. Med.* 28/9, 86, 1950. — 6. Dock, W.: *J. A. M. A.* 140, 1135, 1949. — 7. Eppinger, H., L. V. Papp and H. Schwarz: *Über das Asthma cardiale. Versuch zu einer peripheren Kreislaufpathologie*. (Berlin 1924.) — 8. Fejfar, Z. and J. Brod: *Čas. lék. čes.* 88, 1352, 1949. — 9. Gollwitzer-Meier, K., K. Kramer and E. Kruger: *Pfl. Arch.* 237, 639, 1936. — 10. Gregersen, M. I. and J. D. Stewart: *Am. J. Physiol.* 125, 142, 1939. — 11. Halmágyi, D., B. Felkai, J. Iványi and G. Hetényi: *Brit. Heart J.* 14, 101, 1952. — 12. Hayward, G. W.: *Lancet* I, 1948, 18.—21. — 13. Herget, R.: *Der Chirurg* 1943, 15, 524. — 14. Howarth, S., J. McMichael and E. P. Sharpey-Schafer: *Clin. Sci.* 6, 41, 1946. — 15. Landis, E. M., E. Brown, M. Fauteux and C. Wise: *J. Clin. Invest.* 25, 237, 1946. — 16. Little, J. M.: *Am. J. Med.* 7, 207, 1949. — 17. Merrill, A. J.: *J. Clin. Invest.* 25, 389, 1946. — 18. Merrill, A. J.: *Am. J. Med.* 6, 357, 1949. — 19. Mokotoff, R., G. Ross and L. Leiter: *J. Clin. Invest.* 27, 1, 1948. — 20. Nickerson, M. and L. S. Goodman: *J. Pharmacol. & exp. Therap.* 89, 167, 1947. — 21. Peters, J. P.: *New Engl. J. Med.* 239, 353, 1948. — 22. Peterson, L. H.: *Circulation* 2, 351, 1950. — 23. Plesch, J.: *Physiology and pathology of the heart*

and blood vessels. Oxford Univ. Press 1937. — 24. Relman, A. S. and F. H. Epstein: Proc. Soc. exp. Biol. & Med. 70, 11, 1949. — 25. Somogyi, M.: J. Biol. Chem. 89, 733, 1928. — J. Biol. Chem. 83, 157, 1929. — 26. Starling, E. H.: The fluids of the body. Chicago 1909. — 27. Starr, I., W. A. Jeffers and R. H. Meade: Am. Heart J. 26, 294, 1943. — 28. Warren, J. V. and E. A. Stead: Arch. Int. Med. 73, 138, 1944. — 29. Warren, J. V. and E. A. Stead: Feder. Proc. 6, 223, 1947. — 30. Wollheim, E.: Klin. Wschft. 7, 1261, 1928.

Explanation of the abbreviations: R. H. D. = rheumatic heart disease; I. H. D. = ischaemic heart disease; H. H. D. = hypertensive heart disease; L. F. = left failure; R. F. = right failure; M. S. = mitral stenosis; M. R. = mitral regurgitation; A. R. = aortic regurgitation.

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The Rôle of Neuro-Humoral Factors in the Genesis of Renal Haemodynamic Changes in Heart Failure.¹

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The classical conception of Starling (17) that congestion of the venous vascular bed behind the failing heart is the principle factor in the genesis of the disturbed water balance in heart failure has been recently questioned by several investigators (9, 12, 19). We have produced evidence (1) that changes of water balance in the body of decompensated cardiacs bear no simple relation to changes of venous pressure and that there is a good correlation between these changes and the changes in renal blood flow. A decrease of the renal fraction of the cardiac output with a diminished blood flow through the kidneys is the cause of the disturbed excretion of water and electrolytes and of their retention in the body, this disturbance being produced both by a reduction of the rate of glomerular filtration and by an increased tubular reabsorption of water, sodium and chloride. In accord with Merrill (9), we found that the main increase in the renal vascular resistance occurred behind the glomeruli. Having been able to exclude venous back pressure as the cause of the high post-glomerular resistance we concluded that the chief reason for this high renal vascular resistance was in the increased efferent arteriolar tone.

Mokotoff and Ross (11) tried to investigate the mechanism of this increased efferent arteriolar resistance by means of a high spinal anaesthesia. They were unable to normalize by this measure the disturbed renal haemodynamics in their subjects with heart failure. Their results are, however, open to question: all their subjects received prior to high spinal anaesthesia an injection of Ephedrine in order to prevent a fall in blood pressure. Gaddum and Kwiatkowski (6) demonstrated that this substance increases the sensibility of the vessels to small doses of Epinephrine. Should Epinephrine or Sympathine *E* be liberated in increased quantities in heart failure, we could not expect any reduction of the increased

¹ A preliminary report of these results was presented at the 1st International Congress of Cardiology in Paris 1950 (published in the Comptes Rendus of this congress).

efferent arteriolar tone following denervation of the kidneys which by itself sensitizes vessels to the action of Epinephrine this sensitivity being further enhanced by Ephedrine.

In a previous paper we have demonstrated that when the heart starts to fail the whole vascular bed is rebuilt. There is not only an increase in the peripheral vascular resistance and in the venous tone but there is also a redistribution of blood which is drawn away from various organs in order to maintain blood supply to some of the vital structures even under these precarious conditions. We have pointed out that all these changes in the circulation are of a reflex origin. It seemed, therefore, worth while to investigate also renal haemodynamic changes from this point of view. As in the observations reported on in the previous paper Dibenamine was used in this study (4). The great advantage of this substance was the long duration of its action which was especially important in subjects with a low urine flow thus making possible a sufficient prolongation of the individual urine collection periods and in this way avoiding errors inherent in incomplete bladder emptying and in the renal dead space.

Methods.

The investigations were carried out in the same 5 normal subjects and in 15 cardiacs at various stages of heart failure in whom the general haemodynamic changes following Dibenamine were reported on in our previous paper (4) together with the details of the experimental procedure.

Renal plasma flow was measured by the p-aminohippurate (PAH) clearance, the rate of glomerular filtration by the clearance of inulin, filtration fraction was calculated as the ratio of these two clearances $\left(\frac{\text{clearance inulin}}{\text{clearance PAH}} \times 100 \right)$. Renal fraction was expressed

as the ratio $\frac{\text{renal blood flow}}{\text{cardiac output}} \times 100$, the value of renal blood flow being calculated from

the PAH clearance and haematocrit and cardiac output measured by the methods described in our previous paper. Chlorides were estimated by van Slyke's modification of Sendroy's method (18), sodium by flame photometer (5). The symbols for electrolyte excretion and reabsorption are the same as those used previously (3).

Results.

All our results are collected in table 1. Data on cardiac output and peripheral vascular resistance reported already in our previous paper are also included in order to clarify the correlation between the haemodynamic changes in the kidneys and in the general circulation. The first row of figures is the average of at least 3 control periods prior to the administration of Dibenamine. Further figures are the average of a varying number of observation periods covering approximatively the first hour of the Dibenamine effect and its later phases. The dividing point between this early and late stage of the Dibenamine effect was the change in renal plasma flow. This contraction of our results proved to be not only space saving but it allowed a better survey of all our results and significant differences became more obvious. As in our previous paper the subjects are grouped according to the degree of heart failure, the first 5 subjects being normal con-

trols. The concentration index of inulin (U/P) indicates how many times inulin became more concentrated on its course from the glomeruli through the renal tubuli to the bladder. It is, therefore, a measure of the degree of water reabsorption from the tubuli. The clearances of sodium or chlorides are especially significant when compared with the clearance of inulin indicating how much of the filtered electrolyte was excreted in the urine. T_{Na} or T_{Cl} indicates directly in m-equivalents the amount of the reabsorbed electrolyte. This figure is calculated as the difference between the electrolyte load and the quantity of excreted electrolyte. The electrolyte load is the quantity of electrolyte filtered and equals the product of glomerular filtration (clearance inulin — Cl. inul.) and plasma electrolyte concentration ($P_{Na, Cl}$) i. e. $P_{Na, Cl} \times Cl_{inul}$. The small factor for Donnan's equilibrium was neglected throughout this work. The ratio of chloride and sodium clearances is an index of the parallelism between tubular reabsorption of these two electrolytes. The ratio $\frac{T_{Na}}{P_{Na} \times Cl_{inul}} \times 100$ indicates the percentage of the filtered sodium reabsorbed in the tubuli.

We have demonstrated in our previous paper that Dibenamine produced a transient increase in cardiac output which was more marked in subjects with heart failure than in normal controls. It may be seen from the table that this transient increase occurred usually in the early phase of the Dibenamine effect whilst it dropped towards the original value in the later phase of our observations. On the other hand the fall of the blood pressure continued usually throughout both these observed phases of the Dibenamine action.

This can be easily followed also in fig. 1, representing the detailed course of events in a 35 years old healthy female (No. 2), who received 10 mg Dibenamine per kg b. w. The peak value of the cardiac output was found some 80 minutes after the start of the Dibenamine infusion. At the same time there was a significant fall in the peripheral vascular resistance. The renal fraction of the cardiac output fell at this early stage of the Dibenamine action. This indicates that the renal vascular bed did not take part in the general reduction of the peripheral vascular resistance. The simultaneous slight increase in filtration fraction makes even an increase of the efferent arteriolar tone plausible. This reduction of the extrarenal vascular resistance coupled with a slight increase of the renal vascular resistance caused the renal plasma flow to drop. The glomerular filtration rate followed more or less parallelly changes in the renal plasma flow. However, marked changes of the renal haemodynamics in the opposite direction occurred from the second hour onwards during the phase of the secondary fall of the cardiac output. Whilst the extrarenal vascular resistance started to rise slightly again, there was a very marked increase in renal fraction of the cardiac output pointing to a great reduction of the renal vascular resistance. The decrease of the filtration fraction indicated a reduction of the efferent arteriolar tone. A consequence of this release of the renal vascular tone was a rise in the renal blood flow. Glomerular filtration rate followed again the changes in the renal plasma flow but on a smaller scale. The urine output paralleled changes of the glomerular filtration rate and the variations of the clearance of sodium were parallel to those of the urine flow.

Thus in the normal subject Dibenamine had no effect on renal vascular resistance in the early stage when extrarenal resistance became already markedly reduced. During the later stage of the Dibenamine action, however, the fall of the renal vascular resistance exceeded that of the extrarenal vessels.

The changes of the renal haemodynamics in normal subjects No. 1 and 3 were analogous, though, especially in subject No. 1, much less marked. They demon-

Table

Changes of cardiac output, blood pressure and renal functions after adrenergic blockade in the disease at various stages

Case number	Initials	Age	Sex	Weight	Diagnosis	Total dose of Dibenamine mg	Dibenamine mg/1 kg b. w.	Time after Dibenamine	Cardiac output ml	Blood pressure mm Hg
a	b	c	d	e	f	g	h	i	j	k
1	M. B.	24	F	61	Normal	500	8	— 0-70' 70-260'	7,210 11,500 7,370	110/65 107/68 101/62
2	M. P.	35	F	50	Normal	500	10	— 0-90' 90-126' 126-230'	6,650 8,940 7,050 3,450	105/75 99/71 95/65 102/70
3	B. M.	35	M	70	Normal	300	43	— 0-27' 27-54' 54-86.5' 86.5-142'	7,592 8,208 — 10,981 10,611	135/95 120/99 115/85 130/85 100/70
4	O. Z.	20	F	73	Normal	350	5	— — 0-30' 30-80'	8,340 8,680 7,020 8,050	130/100 145/65 145/78 135/82
5	O. S.	23	F	59	Normal	300	5	— — 0-60' 60-100'	6,250 6,830 8,400 5,650	135/100 199/85 130/78 115/75
6	F. V.	42	M	55	R. H. D.; M. S., comp.	250	5	— — 0-55' 55-110'	3,990 5,015 3,970 6,170	120/75 110/75 117/77 105/65
7	A. G.	39	M	65	R. H. D.; M. S.; A. R.; Fibril. Comp.	250	3.85	— — 0-25' 25-74' 74-106'	11,586 11,610 8,430 17,400 13,750	123/88 130/85 127/82 118/80 105/70
8	F. P.	51	M	59	Emphysema pulm. — Cor pulm. R. F. + —	45	DHE	— 0-20' 20-40' 60-160'	6,300 — 7,540 8,480	120/80 115/85 120/80 125/97
9	J. B.	58	M	71	Endomesaortitis Lu.; I. H. D.; L. F. + —	350	5	— 0-80' 80-260'	6,100 7,930 7,210	200/45 188/35 164/30
10	J. K.	40	M		Auricular septal defect. — R. H. D.; M. R.; R. F. + —	200	4	— 0-41' 41-102'	5,700 7,840 6,585	170/110 170/100 110/80

1.

Dibcnamine or Dihydroergotamine (DHE 45) in normal subjects and subjects with heart of heart failure.

Urine output V ml/1 min.	Clearance PAH ml/1'	Renal fraction %	Clearance inul. (Cl inul. ml)	Filtration fraction %	Inulin concentra- tion index U/P	Sodium clearance Cl _{Na} ml/1 min.	Sodium reabsorbed m-Eq/1 min. T _{Na}	$\frac{Cl_{Na}}{Cl_{inul.}}$	$\frac{Cl_{Cl'}}{Cl_{Na}}$	$\frac{T_{Na}}{P_{Na} \cdot Cl_{inul.}} \times 100$
l	m	n	o	p	q	r	s	t	u	v
0.75	443	9.91	107.9	25.1	144.35	0.9965	14.8550	0.924	—	99.075
0.54	470	7.53	106.7	23.4	193.60	0.8023	15.1506	0.736	—	99.266
0.264	330	7.28	84.8	25.0	325.25	0.1510	11.9280	0.179	—	99.820
0.46	433	10.90	72.1	16.7	158.1	0.280	9.252	0.392	—	99.610
0.41	429	8.75	68.5	16.1	167.9	0.200	8.523	0.293	—	99.796
0.102	241	5.50	41.4	17.2	404.0	0.030	5.150	0.073	—	99.930
0.524	518	18.50	74.8	14.25	178.9	0.198	9.165	0.230	—	99.760
2.02	666	17.2	139.4	21.15	70.1	—	—	—	—	—
1.275	388	8.8	98.5	25.4	77.3	—	—	—	—	—
1.15	460	9.0	119.8	26.0	104.2	—	—	—	—	—
1.678	510	8.5	93.5	18.3	137.9	—	—	—	—	—
0.396	726	12.4	100.5	13.85	254.0	—	—	—	—	—
1.70	478	9.81	120.0	20.0	103.3	*1.280	*12.707	*1.070	—	*98.890
2.56	666	11.90	136.0	20.4	53.1	*4.618	*14.715	*3.395	—	*96.605
2.79	718	15.18	116.2	16.18	41.6	*4.880	*12.245	*4.199	—	*95.801
1.60	794	17.80	109.25	13.97	76.5	*2.557	*11.321	*2.316	—	*97.684
1.11	328.5	8.78	86.3	26.3	78.0	*2.350	*9.180	*2.710	—	*97.30
0.595	348	7.21	101.3	29.2	170.5	*0.506	*10.886	*0.499	—	*99.501
0.39	524	10.43	93.15	17.78	238.25	*0.321	*9.975	*0.344	—	*99.652
0.20	308	7.16	63.0	20.5	315.0	*0.107	*6.604	*0.169	—	*99.831
0.690	249	11.11	70.8	28.5	102.8	*1.210	*7.760	*1.690	—	*98.300
1.335	294	10.53	67.8	23.1	50.8	*0.660	*7.217	*0.973	—	*99.020
0.95	257	10.59	69.3	26.7	72.85	*1.087	*7.128	*1.569	—	*98.425
0.289	100.5	2.93	35.2	35.0	121.7	*0.229	*3.672	*0.650	—	*99.350
0.84	418	7.27	85.3	20.8	106.3	0.21466	13.050	0.253	261.7	99.746
0.608	279	4.68	64.1	22.9	105.5	0.975	9.600	0.152	196.4	99.848
0.624	252	5.82	83.3	33.1	133.5	0.2206	11.631	0.265	81.3	99.736
0.456	193	2.52	73.9	38.2	164.6	0.2699	10.796	0.360	62.4	99.640
0.406	244	3.51	90.5	37.1	223	0.1007	14.690	0.111	74.4	99.881
0.677	235	9.82	84.8	36.2	126.8	0.800	12.422	0.863	—	99.141
0.448	283	12.23	92.5	32.6	206.0	0.344	14.008	0.371	—	99.630
0.515	287	10.25	117.8	41.0	228.5	0.308	17.153	0.261	—	99.738
0.69	233	7.95	100.0	42.75	146.25	0.311	14.720	0.309	—	99.7895
0.55	356	9.70	88.1	24.8	137.4	2.83	12.019	3.226	29.441	96.777
0.56	330	6.89	86.3	26.3	159.7	3.017	11.389	3.351	29.053	96.496
0.38	365	7.97	75.1	20.8	202.1	0.562	11.64	1.422	86.349	99.2249
0.90	313	10.07	116.2	34.75	129.3	—	—	—	—	—
1.54	428	10.05	125.2	29.2	81.4	—	—	—	—	—
0.473	484.5	13.22	106.05	21.9	240.0	—	—	—	—	—

Case number	Initials	Age	Sex	Weight	Diagnosis	Total dose of Dibenamine mg	Dibenamine mg/kg b. w.	Time after Dibenamine	Cardiac output ml	Blood pressure mm Hg
a	b	c	d	e	f	g	h	i	j	k
11	J. K.	48	M	56	R. H. D.; M. S.; R. F. ++	300	5	— — 0—50' 50—80'	1,388 1,600 1,698 1,510	160/120 145/100 125/95 130/90
12	J. Š.	59	M	103	I. H. D.; H. H. D.; R. F. ++	500	5	— 0—110'	6,320 9,930	190/125 200/115
13	J. B.	48	F	71	R. H. D.; M. S.; A. R.; Fibril.; R. F. ++	350	5	— 0—50' 50—140'	2,000 1,955 2,960	133/110 135/112 117/88
14	M. P.	70	F	49	I. H. D.; R. F. ++	500	10	— 0—70' 70—370'	2,645 4,030 3,050	138/80 142/70 118/65
15	M. H.	67	F	47	I. H. D.; L. F.; R. F. ++	500	10	— 0—70' 70—132' 132—218' 218—326' 326—430'	3,445 4,000 4,200 5,140 5,070 3,450	172/80 165/77 165/70 123/68 116/60 108/61
16	B. D.	56	F	67	R. H. D.; M. S.; Fibril.; R. F. +++	300	5	— 0—70' 70—118' 118—176'	2,260 2,630 4,200 3,200	95/60 90/70 90/65 95/60
17	R. K.	70	F		I. H. D.; Fibril.; L. F.; R. F. +++	200	3.25	— 0—21½' 21½—101½' 101½—133'	3,361 3,400 4,900 4,120	125/101 175/100 160/85 110/60
18	S. Š.	69	M	66	H. H. D.; I. H. D.; R. F. +++	300	4.55	— 0—21' 21—82'	2,757 3,280 8,550	213/163 250/191 233/127
19	M. P.	46	F	50	R. H. D.; M. S.; M. R.; Tricusp. regurg.; R. F. +++	250	5	— — 0—26' 26—49' 49—84' 84—120'	2,918 3,912 — — 3,620 3,386	150/70 170/80 152/77 143/77 135/75 126/65
20	A. K.	61	M	67	Cor. pulm.; R. F. ++++	400	5	— 0—110'	3,805 9,070	165/115 193/120

* Chloride instead of sodium.

strate that in normal subjects the blocking of adrenergic impulses has an earlier and more pronounced effect in the extrarenal than in the renal vascular bed.

The changes in subjects No. 4 and 5 were somehow different. These subjects, although healthy, displayed a marked anxiety throughout the course of our ob-

Urine output V ml/1 min.	Clearance PAH ml/1'	Renal fraction %	Clearance inul. (Cl inul. ml)	Filtration fraction %	Inulin concentra- tion index U/P	Sodium clearance Cl _{Na} m/1 min.	Sodium reabsorbed m-Eq/1 min. T _{Na}	$\frac{Cl_{Na}}{Cl_{inul.}}$	$\frac{Cl}{Cl'}$ $\frac{Cl_{Na}}{Cl_{Na'}}$	$\frac{T_{Na} \cdot Cl_{inul.}}{P_{Na}} \times 100$
l	m	n	o	p	q	r	s	t	u	v
0.45	138.0	20.25	54.4	40.0	110.5	*0.544	* 5.66	*0.954	—	*99.1
0.405	141.0	18.2	62.0	44.0	153.0	*0.265	* 6.49	*0.427	—	*99.5
0.546	174.2	21.1	56.0	32.3	102.6	*0.445	* 5.82	*0.797	—	*99.3
0.406	206.0	25.2	49.3	23.9	121.4	*0.229	* 5.48	*0.465	—	*99.6
0.886	339	8.63	172	50.8	194.5	*1.193	*18.57	*0.692	—	*99.4
2.31	427	8.27	183.3	42.93	79.43	*3.397	*19.65	*1.84	—	*99.233
0.22	134	13.79	69.3	50.9	311.3	0.209	9.493	0.299	—	99.709
0.328	139	12.00	65.2	46.8	200.0	0.389	6.049	0.885	—	99.118
0.76	195	14.72	92.0	47.4	119.4	1.170	12.119	1.298	—	98.720
0.771	156	11.53	60.0	38.6	80.1	*0.612	* 5.741	*1.004	—	*99.1
0.434	114	6.39	46.7	40.85	108.9	*0.387	* 4.33	*0.830	—	*99.2
0.295	197	13.88	63.6	33.3	223.1	*0.200	* 5.96	*0.297	—	*99.8
0.46	314.0	14.9	71.3	23.0	153.4	*0.100	* 7.30	*0.139	—	*99.8
0.403	390.0	16.5	72.8	18.9	179.5	*0.111	* 7.54	*0.155	—	*99.8
0.185	285.0	11.6	55.0	19.75	302.0	*0.056	* 5.667	*0.102	—	*99.8
0.23	243.5	8.17	51.8	21.3	224.0	*0.050	* 5.18	*0.963	—	*99.9
0.18	209.0	7.13	41.5	19.95	234.5	*0.040	* 4.05	*0.97	—	*99.9
0.19	176.0	8.63	42.7	24.3	228.0	*0.037	* 4.38	*0.88	—	*99.9
0.09	53.2	4.32	21.4	40.2	231	0.011	3.208	0.051	—	99.937
0.26	111.9	7.85	42.2	37.6	177.5	0.051	6.41	0.106	—	99.9
0.61	118.0	5.16	51.0	43.1	82.7	0.160	7.92	0.31	—	99.68
0.415	104.7	5.44	39.6	37.7	95.1	0.084	6.22	0.21	—	99.79
1.20	173	7.88	64.1	37.7	53.2	—	—	—	—	—
1.27	189	9.47	79.6	42.1	62.7	—	—	—	—	—
1.33	171.5	6.38	53.4	31.0	39.5	—	—	—	—	—
0.369	207.5	8.30	35.2	17.0	95.5	—	—	—	—	—
0.243	48.80	3.4	21.1	43.3	91.8	0.021	2.838	1.099	299.3	99.9
0.222	42.3	2.47	13.1	31.0	59.0	0.024	1.752	0.184	286.8	99.8
0.733	94.5	1.99	26.3	27.8	46.9	0.0833	3.747	0.323	153.4	99.7
0.244	127.9	6.01	51.4	40.4	207	0.277	7.4861	0.525	85.796	99.475
0.176	103.8	5.32	37.0	35.8	110.3	0.160	5.16	0.425	93.25	99.58
0.207	108.6	6.08	39.3	36.1	189.5	0.2543	5.6421	0.6471	72.1195	99.3546
0.043	18.1	0.931	6.22	34.3	144.5	0.01366	0.9183	0.2196	68.3455	99.7534
0.32	121.2	5.5	46.5	38.4	145.3	0.40197	6.8916	0.8644	94.211	99.1363
0.50	196.5	9.56	74.6	37.9	149.0	0.6998	10.7156	0.9381	112.9894	99.0626
0.78	99.3	8.43	62.3	62.65	80.05	*0.306	* 6.308	*0.492	—	*99.508
1.16	134	5.57	68.97	51.67	60.3	*0.716	* 6.654	*1.0255	—	*98.980

servation and special notice of them was made already in our previous paper. The changes in these two subjects were analogous to those found in subjects with heart disease and they will be discussed later.

The detailed sequence of events in a subject with heart failure due to an

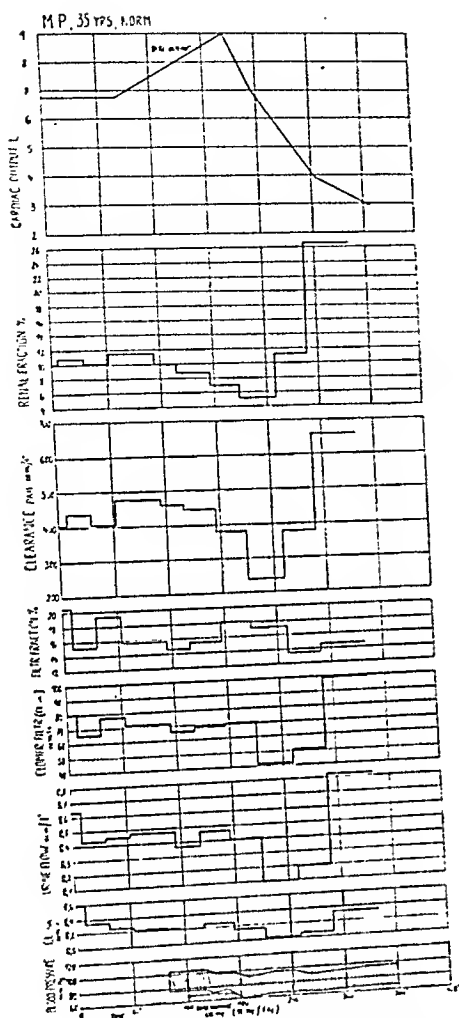


Fig. 1. Changes in cardiac output, blood pressure, renal haemodynamics and function in normal subject after Dibenamine.

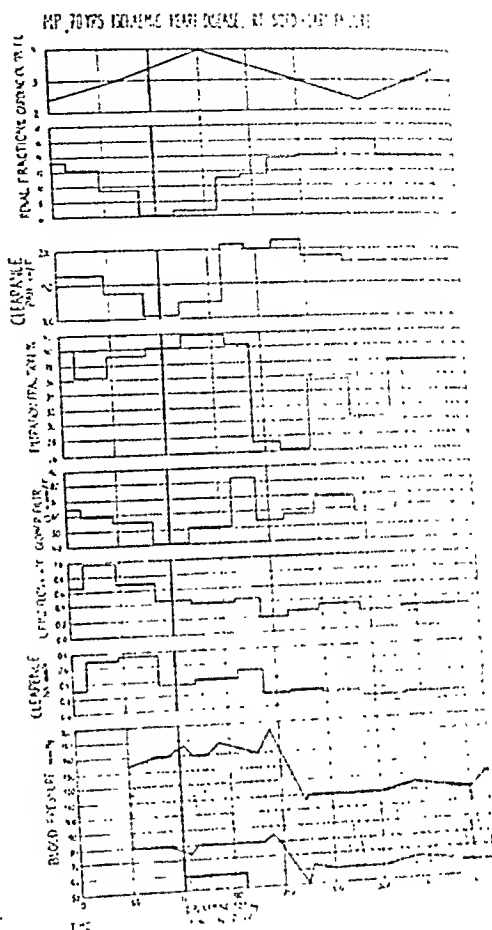


Fig. 2. Changes in cardiac output, blood pressure, renal haemodynamics and function in subject with heart failure, after Dibenamine.

ischaemic heart disease with a relative tricuspid regurgitation (No. 14) is demonstrated in fig. 2.

This subject and subject No. 15 received a relatively large dose of Dibenamine — 10 mg per kg b. w. The changes of the cardiac output and of the peripheral vascular resistance resembled those in normal subjects with the exception that the drop in the peripheral vascular resistance was more marked and persisted also in the second phase of the Dibenamine action *i. e.* during the secondary fall of the cardiac output. Also here renal fraction clearance was lower than during the control period at the time when the cardiac output reached its peak. This demonstrates again that the kidneys partook very little or not at all in the

initial drop in peripheral vascular resistance. In the consequent periods, however, there was a steady rise in the renal fraction of the cardiac output and at the same time the renal blood flow started to increase to a value exceeding by as much as 50 % the last value immediately prior to the administration of Dibenamine. The marked drop of the filtration fraction which occurred at the same time points to a relaxation of the efferent arteriolar resistance as the cause of this increased renal blood flow. Because of the marked drop of pressure in the glomerular capillaries during the phase of increased renal blood flow, the glomerular filtration rate changed relatively very little in comparison with its original values. It was surprising that the improved renal circulation was not connected with any increase in the urine flow. On the contrary oliguria became even more marked during the second phase of the Dibenamine action, urine flow falling to as little as 0.2 to 0.3 ml per minute. The parallelism of the sodium clearance with the rate of the urine flow noted already in the normal subjects was maintained also in these decompensated cardiacs.

A similar trend of events is also well evident in one of our most severely ill patients M. P. (No. 19), a 46-year-old female suffering from rheumatic heart disease with mitral stenosis and incompetence with a relative tricuspid regurgitation and right sided heart failure, who received 5 mg Dibenamine per kg b. w. (fig. 3). One hour after the start of the infusion of Dibenamine a 20 % rise in cardiac output and a simultaneous reduction of the blood pressure pointed to a released peripheral vascular resistance. The delay in the reduction of the peripheral vascular resistance was well evident especially in the period between the 26th and the 49th minute when a marked drop of the renal fraction of the cardiac output occurred. Between the 48th and 84th minute when cardiac output reached its peak the renal fraction of the cardiac output and renal blood flow were at their original values. At this stage of the observation the reduction of renal vascular resistance was evidently of the same degree as the reduction of the extrarenal vascular resistance. After the 84th minute the cardiac output started to decline. In this moment a marked rise of the renal blood flow occurred coupled with an increase of the renal fraction of the cardiac output to almost double its value. Thus, at this later stage of the Dibenamine effect, the fall of the renal vascular resistance exceeded that of the extrarenal vascular resistance. The changes of the filtration fraction were less marked in this subject. Consequently, the rise of the renal blood flow was accompanied by a rise in the rate of the glomerular filtration. Results in this subject differed from those in the previous one by an increase in the urine flow and in the sodium output. Results in these two subjects are representative of the behaviour of all the subjects studied.

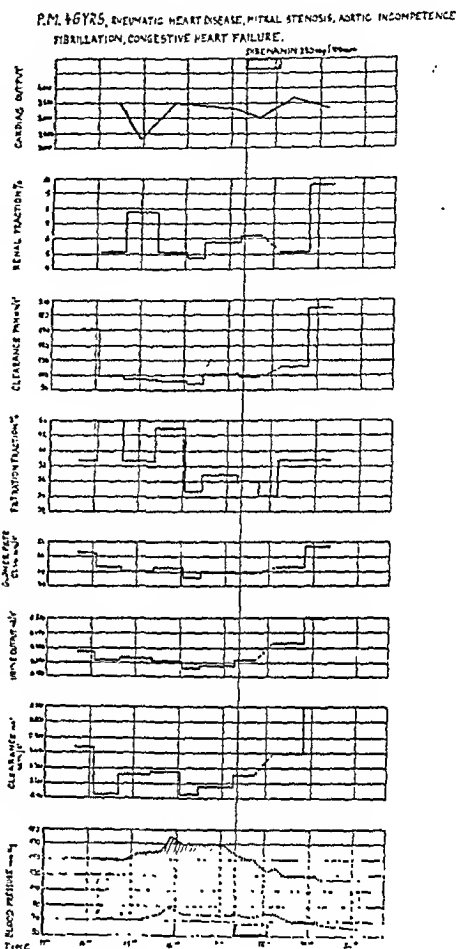


Fig. 3. Changes in cardiac output, blood pressure, renal dynamics and function in subject with heart failure, after Dibenamine.

A detailed analysis of the results in table 1 reveals the following points:

1) *Renal plasma flow*: In subject J. B. (No. 9) with a slight degree of heart failure, renal plasma flow did not change significantly following Dibenamine. In 2 normal subjects (No. 1 and 2) and 2 compensated cardiacs (No. 6 and 7) there was a drop of renal plasma flow by more than 10 % of its original value, although in subject M. P. (No. 2) a rise occurred later on. In the normal subject B. M. (No. 3) a similar biphasic change of renal plasma flow was noted. In the remaining 2 normal control subjects and in 12 of the 13 decompensated cardiacs renal plasma flow increased 19 to 121 % of its original value. It should be noted that the two healthy subjects whose renal plasma flow increased following Dibenamine were those previously mentioned with marked anxiety throughout the course of the observation.

2) *Filtration fraction* did not change significantly in the 2 normal subjects M. B. and M. P. (No. 1 and 2) and rose along with the fall of renal plasma flow in the 2 compensated cardiacs F. V. (No. 6) and A. G. (No. 7). It decreased significantly in the two healthy subjects with anxiety (No. 4 and 5), further there was a late decrease of the filtration fraction in the normal subjects H. M. (No. 3) and in all 13 decompensated cardiacs. However, only in 4 cardiacs in failure (No. 8, 10 and 17) was it possible to reduce the filtration fraction towards normal values. In the remaining cardiacs filtration fraction remained above the upper limit of the normal range, i. e. above 23 %.

3) *Renal fraction of the cardiac output*: This value depends on relative changes of the cardiac output and of the renal blood flow. As pointed out previously, there is an initial rise of the cardiac output after Dibenamine followed by a secondary drop. It seemed, therefore, necessary to analyse the changes in the early phase of the Dibenamine action separately from those occurring later. During the rising phase of the cardiac output, renal fraction fell in 11 out of the 20 investigated subjects (3 normal, 1 compensated and 7 decompensated cardiacs), it remained unchanged in 3 (1 compensated, 2 decompensated cardiacs) and it increased in 6 subjects (2 normal subjects, both revealing marked anxiety, and 4 decompensated cardiacs). The later phase of the Dibenamine action was observed in 12 subjects. Renal fraction increased in 2 normal subjects and in 6 decompensated cardiacs, whilst a decrease was noted in the remaining 1 healthy subject, 1 compensated and 2 decompensated cardiacs. Contrasting with these rather irregular changes of the renal fraction were the above mentioned changes of the filtration fraction. Its fall connected with the increase in renal plasma flow was noted already during the early phase of Dibenamine action in 11 out of the 13 decompensated cardiacs, in 5 of whom there was a simultaneous decrease of the renal fraction. In the remaining 2 decompensated cardiacs these renal haemodynamic changes occurred later on during the decreasing phase of the cardiac output and in subject M. P. (No. 13) they reached their peak at a time when the values of the cardiac output resembled those of the control period. Also in subject J. K. (No. 11) filtration fraction fell markedly during this later phase of the Dibenamine action when the cardiac output fell from 1,698 to 1,510 ml per minute, a value slightly below that at the beginning. It may be concluded that renal vascular resistance decreased following Dibenamine in all the decompensated cardiacs without exception, although its reduction occurred usually at a different time than the maximum reduction of the extrarenal vascular resistance. Of the 5 normal subjects a definite reduction of the renal resistance was noted only in subjects O. S. and O. Z. (No. 4 and 5) who were anxious and tense, whilst in subject B. M. (No. 3) the initial renal change following Dibenamine was efferent arteriolar constriction evidenced by a decrease of renal blood flow and an increase of the filtration fraction, followed only some 90 minutes later by a relaxation of this increased tone.

4) *Glomerular filtration*: Its changes were irregular and usually only of a minor degree. This was due to the fact that the rate of the glomerular filtration is the resultant of the volume of the renal plasma flow and of the pressure in the glomerular capillaries which changed after Dibenamine in the opposite direction.

5) *Urine flow* did not change in a consistent manner after Dibenamine. In 8 decompensated cardiae who received 5 mg Dibenamine per kg b. w. or less urine flow increased with the increase in renal blood flow. It fell in 1 cardia where renal haemodynamics remained unaffected by Dibenamine (J. B., No. 9) and it also fell in a decompensated subject R. K. (No. 17) whose renal blood flow exhibited only a slight rise following Dibenamine. Of the remaining 3 decompensated cardiae (No. 8, 14 and 15) two received a double dose of Dibenamine (10 mg per kg b.w.) and in the third one (No. 8) the adrenergic blockade was accomplished by Dihydroergotamine. In these 3 subjects urine flow fell at the time when the renal blood flow increased. In the 2 fully compensated cardiae whose renal blood flow decreased following Dibenamine, there was a parallel fall in urine flow. In the 5 normal subjects there was a decrease of urine flow following Dibenamine irrespective of the changes in renal blood flow and of the dose of Dibenamine.

The rate of urine flow is a result of the magnitude of the rate of glomerular filtration and the degree to which this glomerular filtrate is reabsorbed in the renal tubuli. Of the two processes the later is usually the more important one in this respect although usually changes of both functions are at play. We have pointed out already that the rate of glomerular filtration changed in an irregular fashion. The changes of the urine flow were, however, always accompanied by opposite changes in the inulin U/P ratio. This demonstrates that the changes in urine flow following Dibenamine were due to a much greater extent to variations of tubular reabsorption of water than to changes of glomerular filtration. This is especially well marked in subjects M. B. (No. 1), M. P. (No. 14) and S. Š. (No. 18).

6) *Electrolyte excretion*: A detailed analysis of the excretion of electrolytes was carried out in 17 out of the 20 investigated subjects. Excretion of chlorides was investigated in 8 subjects, excretion of sodium in another 5 subjects and excretion of both electrolytes in the remaining 4. This was done because we have demonstrated in a previous paper (5), in accord with others (7) that the excretion of sodium does not always parallel that of chloride and that in a detailed investigation of the electrolyte household sodium clearance cannot be replaced by the clearance of chlorides. On studying the excretion of electrolytes during spontaneous changes of urine flow in cardiae we have found that the quantity of excreted chlorides does not only depend on the tubular chloride load ($P_{Cl} \times Cl_{tubul}$) which at almost fixed plasma concentrations parallels changes of the glomerular filtration but in the first place on changes in urine flow. At low urine flows more electrolyte is reabsorbed in the distal tubuli and the amount excreted decreases (3).

It is apparent from the table that in 11 out of the 17 subjects (No. 1, 2, 5, 6, 9, 12, 15, 16, 18, 19, 20) the changes of clearances of sodium and chloride paralleled changes of both urine flow and glomerular filtration. In the remaining 6, however, there is no parallelism whatsoever between the clearance of electrolytes and the rate of glomerular filtration although the parallelism with the urine flow remains more or less preserved. Even there, where changes in the electrolyte clearance and the rate of the glomerular filtration are in the same direction, they are of a different order. This can be well seen in column *t* of the table containing data of the changes of the clearance ratio sodium (or chloride)/inulin. This ratio increases when urine flow increases and vice versa. This proves again that the electrolyte clearance is linked in the first place with changes in urine flow. The same point is born also by data in column *v*, indicating the percentage of the filtered chloride or sodium reabsorbed in the tubuli. The variations of this value are of a minor order, the majority of figures being in the neighbourhood of 99 %. It is just because of this high rate of electrolyte reabsorption that minor changes in this rate of reabsorption are followed by major changes in electrolyte excretion. This is also the reason for the virtually linear relationship between the electrolyte load or the rate of the glomerular filtration to which this value is proportionate and between their reabsorbed quantity (Mokotoff, Ross and Leiter 12, Fejfar and Brod 3).

In the 4 subjects in whom excretion of both sodium and chloride was studied, their clearance ratio differed almost always from 1. Moreover, in 1 and the same subject this

clearance ratio varied significantly in the course of the observation. This shows again that both these electrolytes are excreted by an independent mechanism.

Discussion.

In our observation we have tried to find an answer to the question whether the same mechanism underlying the changes of the general haemodynamics in heart failure is also at the root of the renal functional disturbance. The interpretation of our results was, of course, made difficult by the fact, that *Dibenamine* and *Dihydroergotamine* which were used in our work did not act on isolated kidneys but affected the whole organism.

When renal vascular resistance changes simultaneously with changes of the cardiac output and vascular resistance of other organs and tissues, the new renal fraction of the cardiac output is the resultant of the respective changes of renal and extrarenal vascular resistance. If the change of the renal vascular bed is of the same order as that in the rest of the body, there is no change in renal fraction and variations in the cardiac output are accompanied by parallel changes of the renal blood flow. If renal vascular resistance decreases compared with other parts of the body, the renal fraction of the cardiac output increases and vice versa. Hence, the renal blood flow is directly proportionate to the cardiac output and indirectly to the ratio $\frac{\text{renal vascular resistance}}{\text{extrarenal vascular resistance}}$. The resistance in the renal vascular bed is due in the first place to the sum of the resistances of the *vas afferens*, *vas efferens* and renal venules.

Following the classical principles of renal haemodynamics laid down by Smith (15) the rise of the afferent arteriolar resistance decreases the renal blood flow and at the same time diminishes pressure in the glomerular capillaries so that the filtration fraction falls. An isolated rise of the efferent arteriolar resistance of the same degree is followed by a similar reduction of the renal blood flow whilst the glomerular capillary pressure rises and the filtration fraction increases. The fall in renal blood flow with a rise of the filtration fraction which is a regular finding in *decompensated cardias*, is thus an expression of an increased efferent arteriolar resistance. That this is true, can be deduced if we take into consideration that renal blood flow in heart failure is diminished. Should under these conditions the efferent arteriolar tone remain unchanged the consequence would be a fall in the filtration fraction. With the glomerular capillary pressure remaining unchanged, the quantity of the glomerular filtrate formed of every 100 ml of plasma flowing through the glomerular capillaries (*i. e.* the filtration fraction) remains unchanged. If renal vascular resistance diminishes by a decrease in the efferent arteriolar tone, there is no need for the renal blood flow to rise, if cardiac output diminishes at the same time, or if, with an unchanged or increasing cardiac output, extrarenal vascular resistance diminishes to a greater extent than the renal vascular resistance. A decrease in the efferent arteriolar tone has as a consequence a decrease of the filtration fraction, but at an unchanged or diminished level of the renal blood flow, this fall of the filtration fraction can be interpreted also as meaning an increase

in the afferent arteriolar tone. If, however, renal blood flow increases at the same time as the filtration fraction falls, the only possible interpretation is a decrease in the efferent arteriolar tone. This follows also from the consideration that an accelerated flow through the glomerular capillaries with an unchanged calibre of the outflow track (*i. e.* of the vasa efferentia) would have as a consequence an increase in the glomerular capillary pressure and of the filtration fraction.

In 12 out of 13 decompensated cardiae the filtration fraction fell following Dibenamine simultaneously with the increase in the renal blood flow. In the light of the above mentioned considerations this points to a decrease of the efferent arteriolar tone during the Dibenamine blockade of adrenergic impulses. In the remaining decompensated cardiae (No. 9), there was no change in the renal blood flow following Dibenamine but there was a similar reduction of the filtration fraction as in the other subjects. However, the renal vascular resistance in this subject was less influenced by Dibenamine than the extrarenal vascular resistance as may be judged from the reduction of the renal fraction. It is, therefore, probable that the fall of the filtration fraction without any change of the renal blood flow was due also in this subject to a decrease in the efferent arteriolar resistance. This subject is thus also brought into line with all the remaining decompensated cardiae. From these consistent results in all 13 subjects with heart failure it may be concluded that the high efferent arteriolar tone which in our opinion causes the renal haemodynamic and functional disturbances leading to water retention and oedema in heart failure, can be diminished by blocking nervous impulses.

The classical interpretation of renal haemodynamics of Smith (15) has been recently challenged by Gomez (8) who tried to evaluate separate resistances of the vas afferens, vas efferens and of the renal venules. According to Gomez vas efferens contributes only little to the increase of the renal vascular resistance in hypertensive disease, the main increase occurring in the vas afferens and in the renal venules. Using these formulas we calculated some of these resistances in our cardiae and found that also here the greatest increase occurred in the vasa afferentia and in the renal venules. Thus in subject M. P. (No. 19) the total renal resistance rose to 37,700 dynes/sec./cm⁻⁵ (normal average 5,310), the afferent arteriolar resistance to 16,190 (normal 1,990), efferent arteriolar resistance to 5,300 (normal 1,660), renal venular resistance to 16,200 (normal 1,660). Following Dibenamine the total renal resistance fell to 20,400 and the afferent, efferent and venular resistances were respectively 7,500, 4,580 and 8,320 dynes/sec./cm⁻⁵. Gomez is undoubtedly right that under altered circulatory conditions the whole renal arteriolar and venous bed takes part in the changes of renal haemodynamics. The fact that at a reduced renal blood flow the quantity of the glomerular filtrate formed from every 100 ml of plasma perfusing the glomerular capillaries increases, whilst afferent arteriolar resistance has increased several times compared with the normal and whilst the mean blood pressure is not increased, requires further clarification. However, if these formulas proved to be correct, they would change only little in the interpretation of our data which under these circumstances would mean that adrenergic blockade reduces the pathologically increased total renal vascular resistance.

From the demonstration that high renal vascular resistance in heart failure can be reduced by blocking nervous impulses, it does not yet follow, however, that these nervous impulses are the cause of the arteriolar spasm in heart failure. We must exclude the possibility that these renal haemodynamic changes following Dibenamine were a secondary consequence of other changes in the body which

were induced by the adrenergic blockade. The high resistance in the renal vascular bed in heart failure is a consequence of the inability of the heart to satisfy the requirements of the body, in other words of an inadequate cardiac output. In our previous paper (4) we reported that the Dibenamine blockade was followed by a considerable, though transient, increase in the cardiac output. It must be decided, therefore, whether the observed decrease of the renal vascular tone following Dibenamine was not a secondary effect of this transient circulatory improvement irrespective of the mechanism through which the renal vascular resistance increases in heart failure. Some facts of our observations would speak in favour of this hypothesis. We succeeded in reducing filtration fraction towards normal values only in subjects No. 9, 10 and 15 whose cardiac output increased simultaneously towards the normal range. A rise of the cardiac output towards normal values (5 to 7 liters) and occasionally even above these figures, was observed also in subjects No. 8, 12, 18, and 20. However, subject J. Š. (No. 12) and S. Š. (No. 18) were suffering from hypertensive disease with nephrosclerosis and the sclerotic changes of the renal vessels might have prevented a reduction of the filtration fraction towards normal values. The other two investigated subjects (No. 8 and 20) were suffering from pulmonary emphysema or pulmonary fibrosis and cor pulmonale. Even when fully compensated, these subjects can satisfy the needs of the body only by increasing considerably the cardiac output. Basic values of 10 to 15 liters under these conditions are not exceptional. These values were not reached in a single of our subjects and it might be that an increase of the cardiac output towards 8,480 ml and 9,600 ml does not correspond to the basic value of these subjects when fully compensated. Should the increase of the cardiac output really be the cause of the fall of the filtration fraction then its only partial diminution following Dibenamine in these two subjects would be no valid proof against this hypothesis.

The results in subjects J. B. (No. 9), M. P. (No. 14), J. K. (No. 11) and R. K. (No. 17) exclude, however, the possibility that the fall of the renal vascular resistance following the blockade of adrenergic impulses by Dibenamine was due to some secondary mechanism brought into play by the increase in cardiac output. In the first 2 subjects the efferent arteriolar tone did not change and it even increased slightly during the increase in the cardiac output. However, when during the later phase of the Dibenamine action cardiac output was returning towards its initial values, the efferent arteriolar tone considerably increased and renal blood flow rose especially in subject M. P. by 26 % compared with its initial value and by 73 % compared with its value at the time when the cardiac output reached its maximum. In subject J. K. whose cardiac output remained very low throughout the whole period of our observation and fell after an insignificant rise from 1,600 to 1,698 ml towards 1,500 ml, the filtration fraction decreased from 44 % to 32.3 % at the peak of the cardiac output and to an almost normal value of 23.9 % during the later fall of the cardiac output. In subject R. K. (No. 17) the filtration fraction fell from 37.7 % to 31.0 % at the time of the greatest rise of the cardiac output, to reach the normal value of 17 % 60 minutes later when the cardiac output fell by almost 1 liter to 4,120 ml. Also in subject B. D. (No. 16) the late fall of the

cardiac output is accompanied by a decrease of the glomerular filtration although it rose transiently shortly after the cardiac output started to fall. Whenever we succeeded in registering this later decrease of the cardiac output in our observations it was never connected with an increase of the renal vascular resistance. We can conclude, therefore, that the decrease of the renal vascular resistance in heart failure occurred independently from simultaneous changes in the cardiac output. We can easily exclude the other two mechanisms which might influence the renal vascular resistance during the Dibenamine effect, *i. e.* the acceleration of the renal blood flow during the rise of the cardiac output and the enhanced secretion of Epinephrine brought about by a fall of the blood pressure. Should the size of the efferent arteriole remain unchanged then the increase of the renal blood flow would cause a rise of pressure in the glomerular capillaries and, consequently, a rise in the filtration fraction. Also Epinephrine, supposing that its renal action was not blocked by Dibenamine, would cause a rise of the filtration fraction and a fall of the renal blood flow, an effect just opposite to that which we have observed. We might conclude, therefore, that changes in renal haemodynamics following Dibenamine are a direct consequence of the blocking of adrenergic impulses influencing renal vessels.

It has to be decided whether the Dibenamine blockade removed the real cause of the increased renal vascular tone in decompensated cardiac or whether the partial reduction of the filtration pressure was due only to the removal of the nervous impulses affecting the basic renal vascular tone. This question is necessary in view of the fact that with a few exceptions Dibenamine did not reduce the filtration fraction towards normal values. A rather voluminous literature is at hand showing that the renal vascular bed is under a considerable vasoconstrictor tone. These conclusions, were, however challenged by Rhoads, van Slyke, Hiller and Alving (14) and Smith, Rovenstine, Goldring, Chasis and Ranges (16) who were unable to produce any change in the renal haemodynamics of normal dogs or normal men by denervation or anaesthesia of the renal pedicle or by a high spinal anaesthesia. Our results are in accord with this view. In 2 normal subjects M. B. and M. P. (No. 1 and 2) there were only insignificant changes of the filtration fraction in the first 70 minutes of the Dibenamine action and renal blood flow remained practically without any change. In both of them extrarenal resistance fell during this phase of our observation. A different behaviour was noted in subject No. 3 and especially in subject No. 4 and 5 who were rather anxious during the course of our observation and whose renal blood flow increased and the filtration fraction fell significantly after Dibenamine. Hence, Dibenamine blockade has only little effect on renal haemodynamics in the kidneys of normal and fully relaxed subjects and it reduced renal vascular resistance in those subjects whose obvious anxiety pointed to an altered function of their nervous system and especially of their cerebral cortex. The type of changes in decompensated cardiaces following Dibenamine was similar to that in subjects with marked anxiety. We may conclude, therefore, that also here Dibenamine did not remove any basic renal vascular tone and that the increase in renal vascular resistance in heart failure was, at least to a great extent, of nervous (adrenergic) origin.

In our previous paper we have demonstrated that the fall of the peripheral vascular resistance after Dibenamine was proportionate to its original elevation. We are unable to offer at the moment any explanation why no such parallelism was found between the degree of the fall of the renal vascular resistance and its original level. It might be that the reactivity of renal arterioles to adrenergic impulses differs from that of the arterioles in other parts of the body. The different reactivity of vessels in different parts of the body to neurohumoral agents is well established. That such a different reactivity of renal arterioles really exists, is born out by the fact, that during the early phase of its action Dibenamine brought down the extrarenal vascular resistance leaving renal vascular resistance unaffected in the majority of instances. On the other hand, renal arterioles seem to react with a much greater intensity to a circulatory break-down in shock (13) and in heart-failure (1, 9). Another possible explanation for the impossibility of reducing renal vascular resistance to normal levels might be sought in the increased production of renin in heart-failure (10). Experiments to decide between these possibilities are so far lacking.

Renal haemodynamic changes produced with Dibenamine in 2 subjects with compensated heart disease are reminiscent of changes encountered in peripheral or central circulatory failure. It is difficult to ascribe these changes at the moment to the hypotension produced by Dibenamine or to an increased production of various humoral agents such as renin (10) or VEM (2). It might be that whilst in heart failure these agents are produced at the maximum rate, so that their secretion cannot be further enhanced by a fall in blood pressure, this homeostatic mechanism might be called into operation in compensated cardiacs when circulation deteriorates. This hypothesis has still to be subjected to experimental proof.

An increase in renal fraction of the cardiac output occurs in cardiacs whenever the efficiency of their heart improves. Such a rise also frequently occurs spontaneously at night (1) and it is accompanied by haemodynamic changes similar to those observed during adrenergic blockade. This spontaneous rise in the renal blood flow is accompanied by an increased urine flow which is partly due to an increase in the rate of glomerular filtration but especially to a diminished reabsorption of water. Were the primary cause of the renal vascular changes removed by the adrenergic blockade we would expect a similar rise of the urine flow. This occurred in 8 out of 11 decompensated cardiac whose renal blood flow increased after Dibenamine. In 7 of them this rise in urine flow was effected by a concomitant change of the rate of the glomerular filtration and tubular reabsorption whilst in the 7th it was produced in the first place by a decrease in the tubular reabsorption. Already when reporting our results we drew attention to the fact that one of the 3 subjects in whom the increase in renal blood flow was not accompanied by any rise in urine flow, received Dihydroergotamine instead of Dibenamine whilst the 2 others received 10 instead of 5 mg Dibenamine per kg b. w. In subject No. 8 and 14 increased renal blood flow was accompanied by a rise in the rate of the glomerular filtration. Hence, the fact that urine flow did not change and even fell, pointed to an increased tubular reabsorption of water. Contrary to decompensated cardiacs there is no parallelism between the rate in renal blood

flow and urine flow in normal subjects (3). The same held true also for changes in urine flow following Dibenamine in our 5 normal subjects. Their urine flow always decreased, although their renal haemodynamics exhibited various and inconsistent changes. This fall in urine flow was due again in the first place to an increase of the tubular reabsorption of water.

It seems, therefore, that Dibenamine has normally an antidiuretic effect acting through an increase in the tubular reabsorption of water this action being reversed in some decompensated cardiae through renal haemodynamic changes favouring enhanced water excretion.

The observed changes in the electrolyte output are in a good accord with our previous findings that distal tubular reabsorption of extracellular electrolytes is influenced by the speed of urine flow through this segment a slow rate of flow allowing a more complete reabsorption and vice versa.

In conclusion we may say that the increased renal vascular tone in heart failure may be reduced by a direct blockade of adrenergic impulses reaching these vessels whilst a normal renal vascular tone remains practically unaffected by such a blockade. It follows that this pathological increase of the renal vascular tone is at least to a great extent of neurohumoral (adrenergic) origin and thus in the same way as the increase in the general arteriolar and venous tone is of reflex nature. This homeostatic mechanism helping to maintain temporarily an adequate blood supply to the heart muscle, to the brain and to the muscles has an adverse effect on renal function. Its consequence, *i. e.* a disturbed water balance with accumulation of salt and water in the body threatens in the end the whole organism.

Summary.

1. In 4 normal subjects and 15 subjects with heart failure the influence of adrenergic blockade with Dibenamine or Dihydroergotamine on renal haemodynamics and function was studied in relation to general haemodynamics.

2. In 2 normal females there was no change in the resistance of the renal vascular bed after Dibenamine. Consequently when cardiac output fell following adrenergic blockade, there was a fall in renal blood flow.

3. In 2 healthy females exhibiting a marked anxiety throughout the course of the experiment renal vascular resistance fell and renal blood flow increased following Dibenamine.

4. Similar changes of renal haemodynamics as mentioned under 3 occurred in 11 subjects with heart failure. In 2 compensated cardiae there was, on the contrary, an increase in renal vascular resistance and decrease in renal blood flow following Dibenamine.

5. The changes in renal vascular resistance after adrenergic blockade were independent of changes in general haemodynamics, *i. e.* of a transient increase in cardiac output and a decrease in peripheral resistance. These were reported in a previous paper.

6. In 8 subjects with heart failure, 1 compensated cardiac and 2 normal females the rate of glomerular filtration changed in parallel with changes of renal blood

flow. The changes of the former were of a minor order than the changes of the latter. In 6 subjects there was no parallelism between changes in renal blood flow and glomerular filtration.

7. Urine flow increased at the same time as renal blood flow increased in 7 cardiacs in failure who received 5 mg or less Dibenamine per kg body weight. In 2 subjects with heart failure who received 10 mg Dibenamine per kg b. w., the increase in renal blood flow was accompanied by a decrease in urine flow. The same effect was noted in 1 cardiac who received Dihydroergotamine and 2 normal subjects. The fall in urine flow was due mainly to an increase in tubular reabsorption of water. Arguments are brought forward to the belief, that this increased rate of tubular reabsorption was due to a stimulation of the posterior lobe of the pituitary gland.

8. The clearance of sodium or chloride changed in relation to changes in urine flow. When urine flow increased, a smaller percentage of filtered electrolyte was reabsorbed than during low urine flow.

9. Sodium and chloride are excreted independently.

10. It is concluded that the increased tone of the efferent arteriole in heart failure and secondary changes of renal function which are due to it are, at least to a great extent, of reflex nature.

References.

1. Brod, J. and Fejfar, Z.: *Quart. J. Med.* **19**, 187, 1950. — 2. Edelman, E. S., Zweifach, B. W., Esehler, D. J. W., Grossman, J., Mokotoff, R., Weston, R. E., Leiter, L. and Shorr, E.: *J. Clin. Invest.* **29**, 925, 1950. — 3. Fejfar, Z. and Brod, J.: *Quart. J. Med.* **19**, 221, 1950. — 4. Fejfar, Z. and Brod, J.: *Acta med. scand.* **148**, 247, 1951. — 5. Fejfarová, M. H., Fejfar, Z. and Brod, J.: *Čas. lék. čes.* **90**, 66, 1951. — 6. Gaddum, J. H. and Kwiatkowski, H.: *J. Physiol.* **94**, 87, 1938. — 7. Goldzieher, J. W. and Stone, G. C. H.: *J. Clin. Endocrin.* **9**, 368, 1949. — 8. Gómez, D. M.: *J. Clin. Invest.* **30**, 1113, 1951. — 9. Merrill, A. J.: *J. Clin. Invest.* **25**, 389, 1946. — 10. Merrill, A. J., Morrison, J. L. and Brannon, E. S.: *Am. J. Med.* **1**, 468, 1946. — 11. Mokotoff, R. and Ross, G.: *J. Clin. Invest.* **27**, 335, 1948. — 12. Mokotoff, R., Ross, G. and Leiter, L.: *J. Clin. Invest.* **27**, 1, 1948. — 13. Phillips, R. A., Dole, V. P., Hamilton, P. H., Emerson, K., Archibald, R. M. and van Slyke, D. D.: *Am. J. Physiol.* **145**, 314, 1946. — 14. Rhoads, C. P., van Slyke, D. D., Hiller, A. and Alving, A. S.: *Am. J. Physiol.* **110**, 392, 1931. — 15. Smith, H. W.: *Lectures on the kidney*. Kansas 1943. — 16. Smith, H. W., Rovenstine, E. A., Goldring, W., Chasis, H. and Ranges, H. A.: *J. Clin. Invest.* **18**, 319, 1939. — 17. Starling, E. G.: *The fluids of the body*. Chicago 1909. — 18. van Slyke, D. D. and Hiller, A.: *J. biol. Chem.* **167**, 107, 1947. — 19. Warren, J. V. and Stead, E. A.: *Arch. int. Med.* **13**, 98, 1911.

Explanation of the abbreviations: R. H. D. = rheumatic heart disease; I. H. D. = ischaemic heart disease; H. H. D. = hypertensive heart disease; L. F. = left failure; R. F. = right failure; M. S. = mitral stenosis; M. R. = mitral regurgitation; A. R. = aortic regurgitation.

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Experiences of Prolonged Cortisone and ACTH Treatment in Rheumatoid Arthritis.

By

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Introduction.

When Hench and his co-workers first reported their experiences of Cortisone and ACTH in rheumatoid arthritis, they took pains to emphasize that these experiences did not entitle the use of these hormones to be regarded as »treatment». The continued development, however, has led to widespread use of these remedies in rheumatoid arthritis and in many other diseases.

It is still a matter of discussion whether ACTH and Cortisone have any established value in the therapy of rheumatoid arthritis. In the long run practical experience will best show the therapeutical value of the preparations. Reports have been presented among others by Boland and his assistants and by Freyberg and his assistants.

In July 1951, Boland presented his findings with 76 arthritic patients who had been treated during a period varying between 6 and 15 months. 27 of the patients were treated for more than one year. In about 2/3 of the cases Boland got a fully satisfactory result. During the Cortone treatment these patients were able to perform their ordinary work, walk and move without help of analgesics. Treatment was interrupted in 16 cases (about 20 %) because of decreasing effectiveness and in 7 cases (about 8 %) because of undesirable side-effects. In about 40 % side-effects of mild and temporary nature were observed which did not force a discontinuation of the medication.

In September 1951 Freyberg and his assistants reported their experiences of prolonged uninterrupted Cortisone treatment in 44 patients with rheumatoid arthritis. 17 of these patients were treated for longer than 6 months, 9 more than 10 months and 4 more than one year. In 82 % of the cases good antirheumatic

effect was obtained: full remission was not attained, but the patients lost their pains and the motility in the affected joints increased. In 4 % of the cases undesirable side-effects forced a cessation of the treatment. Slight and transient side-effects were observed in about half the cases. Cortone therapy, however, could be pursued.

The Present Investigation.

In the Central Hospital, Örebro, between 1951—1953 about 50 patients suffering from rheumatoid arthritis have been treated for shorter or longer periods with ACTH and Cortisone, chiefly the latter, and it seems to be of interest to present our material. 20 patients have been treated for a prolonged period and only these are mentioned here. 16 of the patients were women and 4 were men. Their ages ranged from 27 to 64 years. The periods of treatment varied, 4 cases have been treated for nine months to 1 year, 12 during 1—2 years and 4 during 2—3 years. Thus most of them have been treated during more than one year. Even one year is admittedly too short a time to estimate the results of a treatment of such a lingering disease as rheumatoid arthritis, but the data for these patients treated for a long time might illustrate the value of the treatment from several points of view.

Cortrophine (Organon) has been used as the ACTH preparation of choice and Cortone (Merck) as a Cortisone preparation. Besides the hormone treatment the patients received low doses of salicylates when necessary, and the treatment has been supported with customary physical therapy such as warm baths and active and passive movements.

The 20 long term patients mentioned in this material have all been treated with Cortone. We started with intramuscular injections in daily decreasing doses (usually 300, 200 and 100 mg). After a short time the patients generally received the preparation in the form of tablets, which enable continued medication at home. We have found that the maintenance dose necessary to abolish pain and permit work ranges between 2—2½ and 3 tablets, corresponding to 50—67.5 and 75 mg. The tablets have been given in 2 or 3 doses. We have not considered it necessary to follow the treatment with more detailed analyses of the metabolic processes but have confined ourselves to the usual clinical methods.

In judging the degree of severity of the cases, the author has followed as closely as possible the instructions given by the American Rheumatism Association.

The cases have been divided into 4 groups: 1) Mild, 2) Moderate, 3) Moderately severe and 4) Severe cases of rheumatoid arthritis.

Among the mild cases were counted those patients who had slight joint symptoms and no destructive changes roentgenologically. They were able to perform their ordinary work and move without impediment.

To the second group (moderate degree of severity) those patients were assigned who had slight destruction of bone and cartilage proved by X-rays. Cases with deformities are not included in this group, but the patients in this group had reduced power of motion in affected joints and sometimes a secondary muscle

atrophy. Cases with extra-articular soft tissue lesions such as rheumatic nodules and rheumatic tendovaginitis are also assigned to this group. To a large extent these patients have been able to do their work but had reduced motility in one or several joints.

To the moderately severe group were assigned those patients who had destructions of cartilage and bone in affected joints, proved by X-rays. They had deformities of joints with subluxation, ulnar deviation, hyperextension etc. but no ankylosis in affected joints. Most of them had a genuine secondary muscle atrophy. These patients were able to perform only a small part or none at all of their daily work and they have generally not been able to dress or eat without help.

The fourth group (severe rheumatoid arthritis) included the cases with ankylosis in affected joints. These patients have not been able to do any work at all nor look after themselves, and they have been either lying in bed or sitting in a wheelchair.

The results of the prolonged Cortone treatment are brought together in the following table:

Severity of Disease	No. of Cases	Improvement			Side-effects								
		Very marked	Moderate	Slight	Increase of weight and moon-face	Changes in carbohydrate metabolism	Oedema	Electro-cardiographic changes	Cutaneous changes	Menstrual disturbances	Skeletal changes	Psychic changes	Activity of peptic ulcer
Mild	1	1	—	—	—	—	—	—	—	—	—	—	—
Moderate	2	2	—	—	—	—	—	—	—	—	—	—	1
Moderately severe	12	7	5	—	2	1	1	1	1	—	—	—	—
Severe	5	—	2	3	1	—	—	—	1	—	—	—	—
Total	20	10	7	3	3	1	1	1	2	—	—	—	1

In order to analyze the result of the Cortone treatment the material is divided into 3 groups: 1) Very marked improvement, 2) Moderate and 3) Slight improvement.

The first group (very marked improvement) comprises those cases who had no remaining indications of rheumatoid activity, no indication of inflammation of joints and no remaining reduction of motility in affected joints. In these patients the erythrocyte sedimentation rate became normal. Deformities depending on irreversible changes of joints have remained. These patients have been able to walk, to be out of bed and to do their work.

To the 2nd group (moderate improvement) are referred those patients who had no other indications of rheumatoid activity than an elevation of erythrocyte sedimentation rate but no signs of inflammation, such as redness and heat in affected joints. A slight swelling of the joint could remain. Deformities of joints depend-

ing on irreversible changes have remained. The patients have been able to get out of bed and to some extent to do their work.

In the 3rd group are collected those patients who had remaining indications of rheumatic activity: elevation of erythrocyte sedimentation rate and swelling of joints even if they presented increased motility. They have been able to walk with the aid of support of crutches, and they have been able to rise from lying to sitting posture. Even if such an improvement is insignificant from a medical point of view it might have great social value for the patient.

Side-effects from Prolonged Cortone Treatment.

Six of the 20 patients developed side-effects at some time during the Cortone treatment, some of them in more than one way. The most common adverse effect we observed was a tendency towards a gain of body weight in patients treated with Cortone. Three of the patients gained more than 10 kg during one year of Cortone treatment. In one of these patients a «moon face» was observed. Here is, however, the possibility that this gain of weight may partly have depended on the increased appetite which appeared after the diminution of pains and the improvement of the general state.

During the Cortone therapy one of the patients developed a diabetic syndrome with considerable glucosuria and hyperglucæmia. We hesitated whether to continue the Cortone treatment and thereby maintain the diabetes or to stop it and risk a considerable change for the worse of the patient's arthritis. We decided to make a pause in the Cortone therapy but after a fortnight the joint symptoms had steadily increased, and we started Cortone again with good effect. The diabetes of the patient still remained but caused no special inconvenience, and we found that the state of the patient was more endurable with a moderate Cortone dose and that it was better to go on with the Cortone therapy in spite of the diabetic complication. The diabetes did not demand insulin. Moreover, this patient had considerable lung changes of tuberculous origin from long ago. No signs of activity of the process were observed.

We noticed a tendency to oedema in one of the patients. The oedema, however, soon disappeared after discontinuation of Cortone for a short period and after giving salt-poor food. Mercurial diuretics were never called for.

In one of the patients angina pectoris pains appeared during the Cortone treatment, and on the electrocardiogram which earlier had been normal there were observed slight changes indicating possible damage to the myocardium. We supplied vasodilantans of the usual type and could in spite of the symptoms continue the Cortone therapy.

Alterations of the skin have been observed in 2 patients. In one appeared a mild hypertrichosis which caused no marked inconvenience and gave no reason to discontinue the preparation. In another patient during the Cortone treatment some small slow-healing wounds appeared on the ankle-joints. After the Cortone was discontinued these healed quickly and shortly afterwards Cortone could be used again with fully satisfactory effect.

None of the female patients developed menstrual disturbances.

During the Cortone therapy practically all of the patients showed a mild euphoria. The general state improved and lust for life returned. No signs of severe psychical alterations were observed.

Signs of osteoporosis or spontaneous fractures have not been observed among the patients in this material.

In one of the patients alarming symptoms were noted from the abdomen (bleeding from the stomach) during the Cortone treatment. The X-ray verified a peptic ulcer. The patient was put on ulcer diet and antacids. Cortone therapy was continued with 50 mg. every other day. Roentgenological examination after one month did not show any signs of ulcer.

Some Case Reports.

As an example of very marked improvement the following case is reported.

Case 1. (Journal no. 08 05 03). A 45-year-old woman who had been suffering from rheumatoid arthritis since she was 39. She was nursed in one of the Hospitals administered by the State Pension Board. She got roentgen treatment and gold injections with temporary improvement. The last years she had an obstinate pain in her joints and pains when moving. Changes were observed in finger-, hand-, elbow-, shoulder- and knee-joints which were swollen and sore. She was admitted to the hospital on March 3, 1952. At that time she had a moderately severe rheumatoid arthritis. Erythrocyte sedimentation rate about 20 mm. At first she was treated with salicylates and physical therapy: no obvious improvement. Later on Cortone treatment was administered with extraordinary effect. Now the patient was able to make some movements, earlier impossible: she could raise her arms straight up, do her hair and button the back of her dress. She could clench her hands perfectly and go down the stairs (which was impossible before). She could pick up things from the floor, her knee-joints slightly bent. She was treated by us for a month and was later discharged for continuous Cortone medication at home. As minimum dose to keep the patient painless 75 mg ($2\frac{1}{2}$ tablets) of Cortone was required.

The patient was checked by us after half a year: still good result without side-effects. Another check after one month. She got along very well. She was able to perform housework except washing. The Cortone dose was reduced from $2\frac{1}{2}$ to 1 tablet (25 mg) a day but she had to take salicylates as a complement. Checking her in September 1952 we found improvement of the general state and the joints. In March 1953 the patient was taken in again for a short period of observation. She reported that she could keep the house, do the shopping, the cooking and the washing. She had raised the dose herself to 3 tablets a day. After she had started with 1 tablet only, pain and soreness had gradually reappeared in nearly all her joints. She was discharged after one week for prolonged uninterrupted Cortone treatment at home. The erythrocyte sedimentation rate kept down about 9 mm. No adverse effects were observed, only a slight joint swelling. Good motility in all joints. This case has received Cortone treatment for almost $1\frac{1}{2}$ year.

As an example of moderate improvement the following case is reported.

Case 2. (Journal no. 09 03 06). A 44-year-old woman was taken ill with rheumatic joint disease at the age of 28. Between the years 1941—1950 she was nursed on several occasions in a State Pension Board Hospital. There she got 10 series of gold injections altogether and temporarily improved. In 1947 she began to be grayish blue in her skin and this was explained as aurosis. The patient herself considered the gold treatment of

great value. Erythrocyte sedimentation rate had also normalized. The result, however, became shorter after every new cure and the patient had to take big doses of salicylates to manage to get on. After 1950 further gold treatment was not risked because of the aureosis.

In March 1951 the patient was admitted to our hospital. Nearly all joints were affected at that time, the patient could hardly walk indoors and not at all out of doors. The disease was characterized as severe because of the deformities in almost all joints. For 3 weeks in March 1951 the patient got daily Cortone injections of 100 mg. The result was striking. The feeling of illness disappeared, she could reduce the salicylate dose and had better appetite. Objectively a redneel swelling of the joints and an increased motility was observed. The erythrocyte sedimentation rate went down from 67 to 15 mm. Discharged home after 3 weeks. The effect lasted about a fortnight. Then the patient gradually grew worse with stiffness and general feeling of illness. After a month she was readmitted and got Cortone injections with fully satisfactory result. The erythrocyte sedimentation rate went down from 79 to 20 mm. Subjective and objective improvement of the joints. For 3 weeks the patient got daily injections of 100 mg. Then we changed to injections every second day for one week and a half, after which the patient was discharged. Even now the effect remained for about a fortnight.

Cortone injections were given again with prompt and striking result. The erythrocyte sedimentation rate went down from 80 to 20 mm. The first two weeks she got 100 mg of Cortone a day, later 100 mg every second day. This dose, however, seemed to be insufficient: the patient got back the joint symptoms with pain and stiffness. The erythrocyte sedimentation rate went from 15 to 28 mm. Then daily injections of 100 mg were administered. She soon became free from symptoms and was discharged in September 1951. At home she had to give herself Cortone injections (tablet form was not yet obtainable).

The patient was later supervised by our out-door department and for the present she takes 50–100 mg daily in tablet form. Since August 1951 and constantly the patient has taken this dose. She has at the most been able to make a pause of 3–4 days in the therapy. The patient can now keep her house tolerably well and be out of bed. This patient has been treated with Cortone for almost 2½ years with good effect without observing any side-effects.

As examples of slight improvement only the following cases are reported.

Case 3. (Journal no. 07 09 30). 46-year-old woman who since she was about 20 had slight joint troubles. Gradually she got accentuated symptoms with swelling, stiffness and pain. She was repeatedly treated at Central Hospital, Örebro between 1939–1942, in 1947, 1949 and 1950, in the intervals at different sanatoria. Treated with gold injections and roentgen with temporary improvement. 1949 implantations of calf pituitary gland and injections of calf pituitary gland with improvement. 1950 the patient was able to walk indoors with support, but not out of doors. She could eat without help and write with difficulty. Testosterone injections were tried and a moderate improvement was temporarily obtained.

In October 1951 she was again admitted to our hospital. At that time she was not able to walk at all and had severe joint deformities with stretch defects in her knee-joints. She went in a wheel-chair. In February 1953 hormone therapy was administered: at first Cortrophine injections were given, later on Cortone. During this treatment increasing improvement. The patient could walk with the aid of sticks, get out of bed and to some extent dress without help. Improvement was obtained after the implantations of calf pituitary gland in 1949, but by no means to be compared with the result of Cortone therapy. After a treatment of 2 months the patient was discharged and started continuous Cortone therapy at home (2–3 tablets à 25 mg daily).

The patient was hospitalized in November 1952. She had only felt slight pains in the joints. She had been able to eat without help but not to dress. She could now get up from lying to sitting posture. Now she got another series of Cortone injections (200 the first day,

200 the following and 100 mg the third day), whereupon we gave the preparation in tablet form (25 mg \times 4). At the same time she got physical treatment. Subjectively considerable improvement. No pain and much more flexible in her joints. She could walk and move with the aid of sticks and «invalid chair». The patient has since been supervised by our out-door department. She still goes on with the Cortone and can be out of bed and walk with support. She can take part in house-keeping. Earlier she was an invalid confined to her bed. The patient now takes 2 tablets a day (50 mg Cortone). She has been treated for about 1½ year and no adverse effects have been observed.

Case 4. (Journal no. 25 09 23). 27-year-old nurse who since the age of 24 suffered from lingering joint disease of gradual onset. Treated with gold injections and salicylates with moderate effect. In April 1950 the patient was admitted to our hospital and treated with Doea and implantations of pituitary material. She improved and had only slight swelling and stiffness in finger- and knee-joints. Later on she spent 2 months in a sanatorium getting physical therapy, roentgen therapy and gold injections. She became worse rather than better.

Cortone was administered in February 1951, at which time the patient suffered from a severe rheumatoid arthritis and was socially much invalidated. For half a year she had not been able to perform her work. After the administration of Cortone an obvious improvement started. The swelling was reduced and she could move her hands fairly well. She was discharged after three weeks and continued with an uninterrupted Cortone treatment at home (25 mg \times 2–3). As long as she took Cortone she felt painless and was able to work. The erythrocyte sedimentation rate went down from 22 to 9 mm.

In June 1951 she reappeared in the hospital for a new series of Cortone injections with improvement. In September 1951 she was nursed in one of the hospitals administered by the State Pension Board for 2 months. Got ACTH and physical therapy and improved. The patient was later controlled in the Medical Clinic of Central Hospital, Örebro. She takes now 2½ tablets = 67.5 mg of Cortone a day. In parallel with Cortone she has to take 2–3 grm of salicylates. Can walk almost without impediment, clenches her hands completely. The erythrocyte sedimentation rate has been about 16 mm. Tendency to oedema observed on one occasion, but lately no side-effects except slightly increased growth of hair on her arms.

This young woman was on the point of being completely invalidated from rheumatoid arthritis. She had just become a certificated nurse when the disease struck her and made it impossible to work and gain a living. In spite of joint deformities with ulnar deviation and swelling of the joints she is able to work as nurse 8 hours a day.

Discussion.

We have found that in rheumatoid arthritis an improvement of joint state is regularly obtained with Cortone. When we have tried to withdraw the preparation, a deterioration has occurred in a few days. As rheumatoid arthritis has a long and often progressive course, Cortone must be administered during a long period. Thus continued Cortone medication at home after treatment in a hospital has become necessary. Since the preparation is still expensive, 50 % of the costs of this medication have been granted by Örebro Läns Landsting (the County Administration). Most of the patients were health-insured which secured the other half of the cost.

In no case have we noted the development of resistance to Cortone.

We have obtained as good an effect by oral medication as by intramuscular injection of the same dose. As a rule, however, the treatment was started with injections. As appears from the table, most of the patients in this material have suffered from severe or moderately severe rheumatoid arthritis. Before the Cortone therapy some of them had been bedridden invalids, but since the hormone treatment has started they have been able to be out of bed, to move and perform their daily work tolerably. Of the 5 severe cases 2 have become moderately and 3 slightly improved. Of the moderately severe cases more than half of them have become markedly improved and the others moderately.

Appreciable side-effects have appeared in about 30 % of the cases. These, however, have all been mild and in no case necessitated the withdrawal of the preparation.

Our purpose in presenting this material has been to show that in many cases it is possible to perform long-term treatment with Cortone successfully in patients suffering from severe or moderately severe rheumatoid arthritis.

We have found that in appropriate cases a considerable improvement of the illness can be effected with Cortone and moreover that it is sometimes possible to render these severely invalidated patients fit to work, wholly or partially.

This improvement could be maintained for a prolonged period with the aid of uninterrupted Cortone therapy. From a medical point of view the cases are not cured, but socially the effect is of great importance for themselves and their families. Most of the patients were housewives.

We consider that, with the aid of Cortone, some of the more or less invalidated patients have been brought back to social life.

Summary.

Long term treatment of selected cases of rheumatoid arthritis is practically possible and may give valuable medical and social improvement. With a moderate dose (50 to 75 mg a day) unfavourable side-effects were seldom or never observed in 20 patients treated for $\frac{3}{4}$ —3 years.

References.

- Edward N. Boland: *Brit. M. J.* 1951: 2: 191 (July 28). — R. H. Freyberg, C. H. Traeger, M. Patterson, W. Squires, C. H. Adams & C. Stevenson: *J. A. M. A.* 1951: 147: 1528. — Cornelius H. Traeger and Robert C. Batterman: *Therapeutic Criteria and Related Aids in Rheumatoid Arthritis* (American Rheumatism Association: Rheumatic Diseases 1952).

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The Syndrome of High-Titre Cold Haemagglutination.

A Survey and a Case Report.

By

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(Submitted for publication October 16, 1953.)

Cold Haemagglutination (c. h. a.) was discovered and described in 1903 (34) and found in human beings in 1918 (12).

Cold haemagglutinins of low titre are to be found in at least 95 per cent. of normal, healthy human beings (32). Pathological titre figures may be found fairly regularly in cases of primary, atypical pneumonia (22, 39), as well as in certain tropical diseases such as trypanosomiasis and tropical eosinophilia (23). High figures are comparatively often found in association with other infections, particularly when they involve the respiratory tract (21). In cases of mononucleosis, cold agglutinins may be found as well as heterophil agglutinins (7, 15, 21), to some extent with a relatively high titre and in association with haemolytic anaemia (15, 18, 57). On rare occasions an abnormal c. h. a. may occur in association with leukaemia (21, 26) or lymphoblastoma (3), or for some unknown reason.

It has gradually become evident that c. h. a. may not only occur as an insignificant phenomenon in association with a variety of different conditions, but may be found with a high titre in patients presenting certain definite symptoms or symptom-complexes independent of the basic disease from which they are suffering.

Thus one may see acute or chronic *haemolytic anaemias* which, as far as one can see, run a course which is independent of actual cold effects, and which also do not seem to be determined by the c. h. a. itself. In some cases the simultaneous existence of haemolysins has been demonstrated.

Further, certain *peripheral, vascular symptoms* and/or *paroxysmal haemoglobinuria* may be present. These manifestations are found to occur only when and if the person concerned is exposed to the action of cold.

Up to 1947, 19 cases of c. h. a. associated with peripheral vascular manifestations, had been published (26).

In addition to these I have found 15 others (1, 8, 10, 14, 27, 29, 33, 35, 42, 48, 49, 52) beside the case I am about to describe.

These patients complain of being abnormally sensitive to cold, on exposure to which they develop acrocyanosis and Raynaud's phenomena. Four of the patients on record (35, 42, 48, 49) developed gangrene of toes or fingers in response to the prolonged action of cold. In some cases a more or less marked tendency to develop thromboses has been observed (1, 30, 40), sometimes with multiple thromboses (40). It is possible that gangrene of the fingers or toes arises in response to small multiple thromboses in these structures.

Paroxysmal cold haemoglobinuria in association with c. h. a. is also fairly rare, although it is possible that cold agglutination is a relatively frequent cause of this condition which is in itself rare (49). In 1943, Stats & Bullowa (48) collected 17 cases to which they added one of their own. In addition to these cases I have found 11 others (4, 15, 18, 29, 42, 49). Most observers have found that haemolysis in association with c. h. a. is independent of complement, and also occurs in serum inactivated by heat in the ordinary way. This is in contrast to ordinary paroxysmal cold haemoglobinuria with a positive Donath-Landsteiner reaction. There have, however, been exceptions (18, 20, 38). It has been demonstrated experimentally that local cooling of a limb is accompanied by intravascular haemolysis (23, 48).

In nearly all the published cases of peripheral disturbances of the circulation, with or without paroxysmal haemoglobinuria, the maximum cold agglutination titre was between 1:500 and 1:3,000, being no greater in the cases in which gangrene set in. There was one exception (48) to this rule, and in this case the titre was 1:32,000. The lowest maximum titre was 1:250. In two other cases (4, 56) titres were found of 1:2 millions and 1:2.6 millions. In other respects, these cases did not differ from the other cases in the intensity or character of their symptoms.

Only a few cases with such very high titres have been put on record (4, 19, 21, 31, 56). The character of the basic disease has varied, and the aetiology has often been obscure, even though the disease has lasted for months or years (4, 31, 56). Several of the cases referred to have presented neither acrocyanosis nor haemoglobinuria (19, 31). It would thus seem that no definite relationship has been established between the magnitude of the cold agglutination titre and the intensity of the symptoms.

In the following case, with Raynaud's syndrome based on c. h. a. with a titre of a hitherto unknown magnitude, there were manifestations which in certain respects differ from those observed in cases published earlier.

An unmarried woman, aged 60, had always enjoyed good health until 1919. It should be noted in particular that she had never presented signs of inflammation of the lungs, liver disease or syphilis. She had never been pregnant and had never received blood by transfusion. There was no family history, and two brothers, still alive, were healthy. In the autumn of 1919 she gradually became more and more sensitive to cold, with Raynaud's syndrome and cyanosis of hands, ears, tip of the nose and cheek when they

were exposed to cold. At the same time she experienced great lassitude and sense of weakness, but never any shivering or marked malaise.

On examination in April 1950, c. h. a. was observed in enormous dilutions of serum, macroscopic agglutination being demonstrable even in a dilution of 1:42 millions at a temperature of 4° C as well as at room temperature. But there was no macroscopic agglutination at 37° C.

Her symptoms increased in intensity, and some improvement in the following summer was succeeded by considerable deterioration in the autumn of 1951 when, in addition to her earlier symptoms, she developed enormous swelling of her ears which were red and oedematous, presenting small and large weeping ulcers. There were similar ulcers on her forehead and temples in a position corresponding to the hat-brim line. On her admission to hospital in November 1950, she also presented quite marked oedema of her feet and lower part of her legs. Her arms showed no oedema or skin changes, but



Fig. 1. Ulcers on the upper arm over an area corresponding to the position of the cuff of a sphygmometer are seen to be covered by crusts.

after her admission to hospital she developed numerous cutaneous-subcutaneous necroses of different sizes with ulcers running round both her upper arms. These ulcers formed stripes embracing the upper arm in a position corresponding to the site of a tourniquet. They corresponded on the other side to the position occupied by the cuff of a sphygmometer (see fig. 1). All these ulcers were covered by dark crusts which were slow to heal.

The fingers were cyanosed at a room temperature as high as 22–23° C, and when the room temperature was lowered a few degrees, the patient developed Raynaud's syndrome, and her ears and nose became cyanosed. She had to wear gloves in bed, and to cover parts of her face with cotton wool so as to avoid irreversible injuries when she happened to be chilled. Her cold agglutination titre had risen to 1:168 millions (whereas in June of the same year it had been 1:5.2 millions).

She has gradually improved in the course of the subsequent three years. The cold agglutination titre has fallen gradually (see table 1). But she still suffers from fairly marked subjective discomfort in the form of Raynaud's phenomena and cyanosis when she is cold. Her ears are apt to develop ulcers in the cold of the winter. Curiously enough, she has never suffered from ulcers on her hands and feet, and she has never developed gangrene. On one occasion in 1950 she may, perhaps, have had an attack of haematuria.

Table 1.
Summary of laboratory data.

Year	Date	Hb. per cent	Red blood count, millions	White blood count, thousands	Retiocytes, per cent.	Blood platelets, thousands	Leucocytes index	Urobilinuria (Schleisinger's test)	Total protein, g/100 ml	Albumin, g/100 ml	Globulin, g/100 ml	Cold agglutinins + 4° C, dilution	4° C	20° C	37° C
1950	24/4	75	3.2	9.58	4.6	330	13	+ 1/20	6.30	4.15	2.15	1:10 ¹⁰	73	—	—
	8/11	82	3.6	13.16	4.6	280	13	+ 1/20	6.11	4.53	1.58	1:10 ¹⁰	40	—	—
1952	28/1	80	4.1	10.2	5.2	440	—	+ 1/20	6.30	4.46	1.86	1:10 ¹⁰	118	10	—
	9/4	80	4.22	7.20	3.3	625	11	+ 1/10	6.35	4.85	1.50	1:10 ¹⁰	112	50	15
1953	15/4	82	4.10	13.2	3.5	—	10	+ 1/10	—	—	—	—	—	—	—
	18/4	—	—	—	3.5	—	10	+ 1/10	—	—	—	—	—	—	—

Haemoglobinuria has never been discovered, and it has not been provoked by exposure of a limb to cold.

On three occasions she has been treated in hospital for her ailment — in April and November 1950 in the Medical Department of the Stavanger Hospital, and in April 1953 at the Medical Department VIII of the Ullevaal Hospital. She has also been examined from time to time under ambulatory conditions. In spite of searching examinations, it has never been possible to discover any explanation for her severe c. h. a. There has been no clinical or radiological evidence of disease of the chest, abdomen or urogenital system. The patient is a virgo. A radiological examination of her skull and spine has shown nothing of significance. The arterial pulse of her limbs is normal and symmetrical. The lower pole of her spleen has been palpable since February 1952. She has all the time presented a quite slight haemolytic anaemia (see table 1 et seq.).

Observations Concerning the Cold Haemagglutination.

It has been difficult to obtain blood for the necessary tests at ordinary room temperature.

The blood stiffened in the needle and glass tubes, assuming a granular appearance. Even when instruments and glass tubes were warmed, it was difficult to obtain enough blood. Punctures for blood had to be undertaken at a room temperature of 28–30° C. or the patient's arm had to be warmed before puncture. By putting the samples of blood promptly into a thermostat at 37° C, some of the contemplated tests could be carried out. Besides, during the first two years, the mechanical fragility of the erythrocytes was so greatly increased that it was very difficult to obtain samples of blood without haemolysis occurring during aspiration, and success was impossible without the above-mentioned procedure involving warming of the patient and of the instruments. Haemolysis set in promptly when the sample of blood was lightly shaken or was centrifuged, or when the glasses were turned upside down a couple of times. When 0-blood corpuscles were added to the patient's serum, they immediately acquired the same property. It was obvious that this change in the behaviour of the 0-blood corpuscles occurred almost instantly at the high cold agglutination titre existing at the time. A series of tests had to be abandoned during this period.

The maximum cold agglutination titre on macroscopic recording after a sample had stood over-night at 4° C was 1:168 millions when ordinary technique and washed

0-blood corpuscles were employed. A similar titre was obtained with the patient's own blood corpuscles or those of other human beings irrespective of their blood group. As long as mechanical injury was avoided, no haemolysis set in even on frequently repeated chilling and warming, whether the blood corpuscles employed were the patient's own or belonged to others of a compatible group.

When series of samples were set up at different temperatures, the turning-point for incipient agglutination was found to be fairly close to 26° C. When the cold agglutination titre was at its highest, and when serum was stored in a refrigerator at 4° C, a jelly-like mass was precipitated, filling the central part of the glass tube, and being surrounded by clear, fluid serum. This jelly-like mass dissolved at once when the serum was put in a thermostat at 37° C. But it did so with difficulty at room temperature. This process recurred when the serum was again put in a refrigerator. The size of this jelly varied in the different glasses, but it was always there, and it existed in all the samples taken during this stay in hospital (November, 1950). It developed more easily and to a greater extent when the precipitation could occur around a small organic focus in the form of a small clot of fibrin or small foreign bodies introduced into a glass.

It should be added that when a sedimentation rate test was carried out at room temperature and at 4° C, the column of blood corpuscles underwent considerable sinking very rapidly, and thereafter stiffened to a mass with a granular appearance, with the result that no further fall occurred (see table 1).

In spite of the high cold haemagglutination titre figures, hyperglobulinaemia was never found on fractional protein determinations (see table 1). But here, too, a reservation must be made with reference to the exceedingly high titre to be found with the ordinary technique, as the following investigation from the State Institute for Public Health showed in May 1950:

Serum in geometrical dilution in the usual way showed the following titres: 37° C : 0, room temperature: 1 : 2²⁴, 5° C : 1 : 2²⁴.

Serum diluted 1 : 1,000 titrated further: 37° C.: 0, room temperature: 0, 5° C.: 1 : 128,000.

An electrophoretic examination was carried out in February 1952 and in April 1953. Both diagrams were fairly similar and showed nothing definitely pathological. At the last examination definite splitting of the beta globulin fraction was found: Total protein 6.11 g/100 ml, of which the albumin was 69.1 %, alpha globulin 1.8 %, alpha₂-globulin 5.1 %, beta₁-globulin 6.0 %, beta₂-globulin 7.1 %, gamma globulin 10.6 %.

Some other tests:

Serological syphilis reactions (Wassermann, MKR. II, Kahn) negative. The thymol test negative, the Gross test negative, Takata-Ara negative, serum formol-gel (Bing) negative, the Paul-Bunnell test negative. Blood type: A₂MRh + (D +). Eosinophil cells: normal cell count. Differential counts showed nothing abnormal.

There was a slight anaemia of the haemolytic type partially compensated by increased blood regeneration (see table 1). A slight degree of splenomegaly had developed. The osmotic resistance of the erythrocytes was normal: Incipient haemolysis at 0.46–0.48, total haemolysis at 0.24–0.26.

On two occasions sternal puncture showed increased normoblastic erythropoiesis, but otherwise no changes (the ratio of nucleated erythrocytes to white blood corpuscles being 1 : 1).

After the patient had been given 1,000 ml of group-0-blood on April 17, 1953, the duration of survival of the transfused cells was determined by differential agglutination (Ashby). Even though the intervals between different determinations was long, the curve obtained (see fig. 2) supplements other haematological data pointing to the existence of a haemolytic process.

During the patient's stays in hospital in 1950, the Donath-Landsteiner test was carried out, and the heat resistance test was repeated several times with the patient's

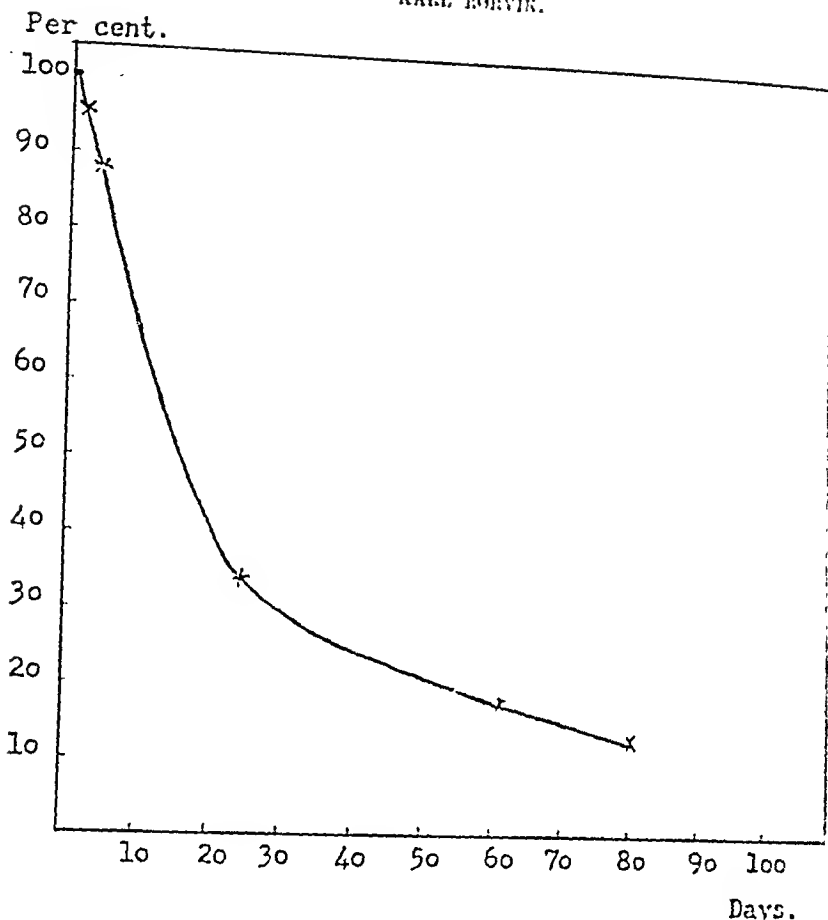


Fig. 2. Survival of the red blood cells after transfusion of 1,000 ml group O blood.

ocagulated whole blood. These tests were negative provided mechanical trauma could be avoided, but the slightest shaking or turning of the glass was promptly followed by haemolysis.

The direct Coombs' test, carried out at the State Institute for Public Health in May 1950, was positive.

During the patient's stay at Department VIII of the Ullevaal Hospital in April 1953, the cold agglutination had fallen to about 1 : 30,000, and at the same time the mechanical fragility of the cells became much less marked. The blood could now be drawn and carefully transported without haemolysis occurring, and certain tests which had hitherto been impossible could now be carried out.

Blood was drawn at a room temperature of 30° C into warmed glasses and placed in thermos flasks containing water at 37° C. After careful transport the samples of blood were examined at the State Institute for Public Health with the following results.

Serum titrated in saline solution against normal O-blood corpuscles and kept for 24 hours at 5° C gave agglutination in a dilution up to 1 : 32,000. The direct Coombs' test carried out on a sample of blood set for coagulation at 37° C was markedly positive (it was impossible to prevent the temperature from falling some degrees below 37° C during centrifuging). The reaction was essentially similar irrespective of whether undiluted

Coombs' serum or serum diluted as for the demonstration of incomplete Rh-antibodies was employed.

When the indirect Coombs' test was carried out in the same way with the patient's serum versus blood corpuscles from 20 different ABO-compatible samples of blood from healthy persons, there was a weaker but definitely positive reaction. There was no reaction in saline solution or albumin versus the same cells at 37° C.

The patient's papainized blood corpuscles were not agglutinated in her own serum at 37° C. Her trypsinized blood corpuscles were not agglutinated in her own serum at 37° C. In a 20 % bovine albumin solution, her cells were not agglutinated in her own serum at 37° C.

Tests were carried out at the blood bank of Ullevaal Hospital with the technique described by Dacie (14 b) with the following results:

Haemolysis tests on the patient's blood corpuscles in acidified normal serum (Ham's test) proved negative. Positive reactions were obtained in tests for haemolysins of the cold type using non-acidified serum (the Donath-Landsteiner test). The tests were stored at -20° C for 7 weeks, and fresh serum complement had to be added in the form of 1/2 volume fresh human serum. The reaction was plainly more markedly positive with acidified serum. On titration of the haemolysins, a titre of 4 was found in non-acidified serum, and a titre of 8 in acidified serum. All the controls were negative, and the test tubes were treated with the greatest caution during the transfer of samples from refrigerator to thermostat. It would therefore seem that haemolysis due to mechanical trauma could be definitely excluded.

Tests for haemolysins of the «warm» type proved negative.

At the hospital's laboratory, attempts were made to demonstrate haemolysin in the patient's urine with the same technique, with and without adjustment of pH — Dacie (14 b and c). An attempt was also made to find out if the addition of fresh normal serum to the urine had any effect. No haemolysins of either the «cold» or «warm» type could be found in the patient's urine.

At the hospital's central laboratory the patient's urine was found to contain haemosiderin, but methaemoglobin could not be found in her whole blood (0.06 g/100 ml).

Discussion.

This 60-year-old woman has suffered for nearly 4 years from well-marked Raynaud manifestations and acrocyanosis on exposure to cold. She has also a quite slight anaemia of the haemolytic type. Her blood serum has contained cold haemagglutinins with an enormous titre, — up to 1:168 millions.

This case differs, however, from cases described earlier not only with regard to the height of her agglutination titre, but also in the matter of the manifestations of her disease.

At the times when she presented the highest agglutination titres, she suffered from prolonged, weeping ulcers on her ears and other parts of her body exposed to cold, particularly such parts as were liable to be pressed on. Such ulcers have not hitherto been described as a consequence of c. h. a. On the other hand, exactly similar conditions have been described in association with high grade cryoglobulinaemia (24, 25, 43). In these cases also there were swelling and ulceration of the lobes of the ears and ulcers of the skin in places exposed to some pressure (43).

In these cases, too, ulcers did not occur on the hands or feet. Our patient also presented reversible jelly-formation in serum kept in a refrigerator for some hours. In other words, her serum fulfils the conditions laid down by Watson &

Lerner (55) for the identification of cryoglobulin. Bearing in mind the prevailing level of the cold haemagglutination titre, it seems natural to assume that the cold agglutinins in this case behaved in the same way as a cryoglobulin. But with the available methods of examination it was not possible to prove the correctness of this assumption. In an earlier case (44) both cold precipitable globulin and cold agglutinin were found.

The haemolytic anaemias existing in association with c. h. a. vary greatly in intensity and in the course they run. In some cases acute haemolytic anaemia run a course which is to a certain extent stormy, and they usually follow a primary atypical pneumonia with a relatively high agglutination titre, sulphonamide having been used (1, 13, 14, 15, 28, 38 a, 41, 42, 47, 49) or not (5, 9, 23, 27). In other cases the anaemias are subacute or chronic, lasting months or years (3, 4, 6, 10, 22, 30, 49, 53, 56, 58) often without any definite basic disease being demonstrable.

It was assumed formerly that haemolytic anaemia was due to intravascular haemolysis provoked by the markedly increased fragility or susceptibility of the erythrocytes to mechanical trauma (16, 47, 52). Experiences in more recent years have, however, challenged this explanation of haemolytic anaemia. Even though there is, as a rule, a roughly parallel situation *in vitro* with reference to the height of the titre and the degree of the haemolysis when such blood corpuscles are exposed to cold and mechanical trauma (47), it has been found that at body temperature conditions are usually different, for now neither agglutination nor haemolysis occurs (47, 56).

Further, the titre may be very high or enormous but without any or with hardly any haemolytic anaemia (4, 19, 47, 49, 56). Conversely, the titre may be comparatively low, but the anaemia severe and rapidly progressive (18, 22, 49, 53, 58). In some cases, however, (53, 58) the agglutinins were active at body temperature also.

There is also no correlation demonstrable between the degree of haemolytic anaemia and the liability to develop haemolytic episodes and haemoglobinuria on exposure to cold (4, 47, 48, 49) and it seems to be difficult to provoke haemolytic anaemia in susceptible patients by exposing them to cold (18).

There is still some uncertainty with regard to the kind of mechanism or process which is operative in the cases in which haemolytic anaemia develops in association with cold agglutination. It has been experimentally demonstrated that the living organism rapidly dissolves erythrocytes exposed to the action of small quantities of haemolysin (17, 54). Dacie (14 c) has demonstrated small quantities of haemolysin in 7 patients whose sera contained a high titre of cold haemagglutinins. In order to demonstrate these haemolysins, it was necessary to correct the pH with small quantities of acid. These substances were cold antibodies with an upper limit for adsorption of about 30° C. They were thermo-stable, and addition of fresh complement was necessary. The titre was far smaller than the titre of the agglutinins present at the same time.

Incomplete antibodies were formed side by side with cold agglutinin and cold haemolysin. The direct Coombs' reaction was positive at 37° C. The indirect

Coombs' reaction was positive after sensitization of normal blood corpuscles at 2—5° C.

In the present case the Donath-Landsteiner reaction was negative at an early date and on frequent repetition. Later on, small quantities of haemolysin were found with or without adjustment of pH. At the same time both the direct and the indirect Coombs' reaction were found to be positive without any chilling of the blood to more than a few degrees below 37° C.

Summary.

With a high degree of cold haemagglutination, a syndrome which is independent of the character of the basic disease may be found. It consists of acrocyanosis, Raynaud's phenomena, gangrene of the fingers, intravascular haemolysis, haemoglobinuria and haemolytic anaemia.

After a general survey of the literature, an account is given of a case with an enormous cold agglutination titre lasting many years and due to some unknown cause. At the same time that the highest titres were measured (1 : 168 millions), the patient presented certain symptoms which have not hitherto been described in association with cold haemagglutination. They consisted of oedematous swelling and weeping ulcers on parts of the body exposed to cold, particularly such as were exposed to a certain degree of pressure. A reversible jelly-formation occurred at the same time in the patient's serum kept in a refrigerator (about 4° C). It may be assumed that there were cold haemagglutinins present in this case behaving as cryoglobulin, as also assumed in a similar case (44).

The patient suffered from slight haemolytic anaemia. Both the direct and indirect Coombs' reaction were demonstrable in blood which at no time had been chilled lower than a few degrees below 37° C.

After the cold agglutination titre had fallen to about 1 : 32,000, small quantities of haemolysin were found both with and without acidification of the serum.

Bibliography.

1. Aaron, R. S.: *Arch. Int. Med.* 89: 293, 1952. — 2. Appleman, D. H. & Morrison, M. M.: *Blood* 4: 186, 1949. — 3. Aubert, A. & Brendemoen, O. J.: *Scand. J. Clin. & Lab. Invest.* 1: 95, 1949. — 4. Bateman, J. C.: *Arch. Int. Med.* 84: 522, 1949. — 5. Battaglia, B.: *Ann. Int. Med.* 27: 469, 1947. — 6. Benians, T. H. C. & Feasby, W. R.: *Lancet* 2: 479, 1941. — 7. Belk, W. P.: *J. Lab. & Clin. Med.* 20: 1036, 1935. — 8. Berlin, K. G.: *Nord. Med.* 41: 28, 1949. — 9. Bending, K. G.: *Nord. Med.* 44: 480, 1950. — 10. Bonnin, H., Dubarry, J., Dulong de Rosnay, Ch. & Lucas, P.: *Sang* 18: 269, 1947. — 11. Boxwell, W. & Bigger, J. W.: *J. Path. Bact.* 34: 407, 1931. — 12. Clough, M. C. & Richter, J. G.: *Bull. Johns Hopk. Hosp.* 29: 86, 1918. — 13. Colmers, R. A. & Snively, J. G.: *New England J. Med.* 237: 505, 1947. — 14 a. Dacie, J. V.: *Sang* 21: 193, 1950. — 14 b. Dacie, J. V.: *Practical Haematology*, Churchill Ltd, London 1951. — 14 c. Dacie, J. V.: *J. Path. Bact.* 62: 241, 1950. — 15. Dameshek, W.: *J. Am. Med. Ass.* 123: 77, 1943. — 16. Dameshek, W. & Miller, E. B.: *Arch. Int. Med.* 72: 1, 1943. — 17. Dameshek, W. & Schwartz, St.: *Medicine* 19: 231, 1940. — 18. Ellis, L. B., Wollenman, O. J. & Stetson, R. P.: *Blood* 3: 419, 1948. — 19. Erf, L. A.: *Am. J. Cl. Path.* 15: 210, 1945. — 20. Ern-

- stone, A. C. & Gardner, W. J.: J. Clin. Invest. 14: 799, 1935. — 21. Favon, C. B.: J. Clin. Invest. 23: 891, 1944. — 22. Finland, M., Peterson, O. L., Allen, H. E., Singer, B. A. & Barnes, M. W.: J. Clin. Invest. 24: 451, 1945. — 23. Ibid. 24: 458, 1945. — 24. Flemberg, T.: Nord. Med. 37: 330, 1948. — 25. Flemberg, T. & Lehmann, J.: Nord. Med. 23: 1565, 1944. — 26. Forbes, G. B.: Brit. Med. J. 1: 598, 1947. — 27. Gellhorn, H. S.: New England J. Med. 234: 826, 1946. — 28. Hegglin, R.: Schweiz. Med. Wochenschr. 76: 105, 1946. — 29. Heilmeyer, L.: Arch. f. Derm. & Syph. 191: 27, 1946. — 30. Heilmeyer, L. & Schubotho: Sang 19, 1948. — 31. Jessen, C. U. & Bött, J.: Acta Med. Scand. 105: 287, 1940. — 32. Kettel, K.: Acta Path. & Microbiol. Scand. 5: 225, 1928. — 33. Kopplin, F.: Ztschr. f. klin. Med. 130: 784, 1936. — 34. Landsteiner, K.: München. Med. Wochenschr. 50: 1812, 1903. — 35. McCombs, R. P. & McElroy, J. S.: Arch. Int. Med. 59: 107, 1937. — 36. Melnikoff, S. M. & Picciotta, A. V.: Ann. Int. Med. 30: 655, 1949. — 37. Moolten, S. E. & Clark, E.: Arch. Int. Med. 89: 270, 1952. — 38 a. Neely, F. L., Baria, W. H., Smith, C. & Stone, C. F. Jr.: J. Lab. & Clin. Med. 37: 382, 1951. — 38 b. Parish, H. J. & McFarlane, R. G.: Lancet 2: 479, 1951. — 39. Peterson, O. L., Ham, T. H. & Finland, M.: Science 97: 167, 1943. — 40. Platt, W. B. & Ward, C. S.: Am. J. Clin. Path. 15: 202, 1945. — 41. Rubin, J. L., Jacobson, A. S. & Meyer, L. M.: Am. J. Clin. Path. 19: 630, 1949. — 42. Ronnqvist-Jessen, V.: Ugeskr. f. Læger 112: 1548, 1950. — 43. Rorvik, K.: Acta Med. Scand. 137: 390, 1950. — 44. Schwartz, T. B. & Jager, B. V.: Cancer 2: 319, 1949. — 45. Singer, K. & Damschke, W.: Ann. Int. Med. 15: 544, 1941. — 46. Stats, D.: Proc. Soc. Exper. Biol. & Med. 51: 305, 1943. — 47. Stats, D.: J. Clin. Invest. 24: 33, 1945. — 48. Stats, D. & Bullock, J. G. M.: Arch. Int. Med. 72: 506, 1943. — 49. Stats, D., Wasserman, L. R. & Reuther, N.: Am. J. Clin. Path. 18: 757, 1948. — 50. Stratton, F.: Lancet 1: 613, 1943. — 51. Turner, J. C., Nisnewitz, S., Jackson, E. B. & Barney, R.: Lancet 1: 765, 1943. — 52. Waldenström, J.: Nord. Med. 20: 2362, 1943. — 53. Wasastjerna, C.: Nord. Med. 37: 115, 1948. — 54. Wasastjerna, C.: Acta Med. Scand. 132: 132, 1948. — 55. Watson, C. J. & Lerner, A. B.: Acta Med. Scand. suppl. 196 (vol. 128): 489, 1947. — 56. Whittle, C. H., Lyell, A. & Gatman, M.: Proc. Roy. Soc. Med. 40: 500, 1947. — 57. Wilson, S. J., Ward, C. E. & Gray, L. W.: Blood 4: 189, 1949. — 58. Young, L. E. & Lawrence, J. S.: Arch. Int. Med. 77: 151, 1946.

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Pernicious Anemia and Cancer of the Stomach.¹

(Preliminary Report.)

By

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Ever since pernicious anemia and gastric carcinoma in the same patient was reported for the first time by Quincke (13), the cause of this coincidence has been the subject of discussion. Some authors have been of the opinion that cancer of the stomach was the primary cause of pernicious anemia (2, 21). Others maintained that the co-existence of pernicious anemia and gastric carcinoma was due to chance coincidence (16, 20).

When the introduction of specific therapy made a sufficiently long follow-up possible, several authors reported typical cases of pernicious anemia in which cancer of the stomach occurred after a symptom-free interval of several years; in these instances, pernicious anemia had to be interpreted as the primary lesion. However, owing to increased longevity — involving higher age groups among the treated patients with pernicious anemia — the risk that they should die of cancer increased (14).

In order to prove an aetiological relationship behind the occurrence of the two diseases in the same patients the incidence of gastric carcinoma in patients with pernicious anemia had to be compared with its incidence among a group of the population corresponding to the patients with pernicious anemia as regards sex, age, and follow-up period.

As to the comprehensive literature on this subject, it is enough to mention that a number of authors (4, 5), perusing series of autopsy reports on patients with pernicious anemia, unanimously state that gastric carcinoma is essentially more com-

¹ This investigation was supported by a grant from National Cancer Institute of the National Institute of Health, U. S. Public Health Service.

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mon in these patients than in others of the same age groups. Similarly, systematic X-ray examinations of patients with pernicious anemia without any gastric symptoms have revealed gastric carcinoma with striking frequency (6, 15). Definite importance must be attached to the prognostic study of patients with pernicious anemia. The follow-up of large groups of patients with this disease for long periods and comparison of the incidence of gastric carcinoma with that in control groups—equivalent with regard to sex, age, and follow-up period—has established that patients with pernicious anemia show an excess mortality from gastric carcinoma. It is striking that a number of authors unanimously report this excess mortality to be about three times the expected mortality (3, 11, 18).

Gastritis has been mentioned as one of the possible causes of the increased incidence of gastric carcinoma. It is known that in pernicious anemia the gastric mucosa is the seat of pathological changes (atrophy with round-cell infiltration). It has been suggested that these changes might be precancerous (8), and it was therefore reasonable to explain the cancer as a result of simple malignant degeneration of the existing gastritis.

It is doubtful, however, whether the explanation is as simple as that. In pernicious anemia the histological mucosal changes are localized to the fundus and body of the stomach (10). The site of gastric tumours in patients with pernicious anemia is still a debated point, and though it has been claimed that the tumours chiefly affect the body or fundus (17), other authors were not able to confirm this (11).

Moreover, recent histological studies militate against any relationship between chronic atrophic gastritis and gastric carcinoma (1, 9). It therefore seems most natural to interpret the gastritis in pernicious anemia as a secondary phenomenon, unrelated to the malignant tumour.

The possible carcinogenic action of the liver preparations has been advanced as one of the causes of the high incidence of gastric carcinoma in patients with pernicious anemia, but this hypothesis does not seem to be supported by any clinical or experimental evidence.

It has been suggested that the frequent co-existence of pernicious anemia and gastric carcinoma might be due to common hereditary factors (6, 11).

Weighty evidence has been advanced to show that inherited factors play a rôle in the onset of pernicious anemia (12), and recent findings seem to indicate that gastric carcinoma is also hereditary to some extent (19).

If common inherited factors can indeed explain why patients with pernicious anemia are more liable to develop cancer of the stomach, the disease would be expected particularly often among the relatives of patients with pernicious anemia.

In addition to several single cases of gastric carcinoma among the relatives of patients with pernicious anemia the following systematic studies have been published:

Zancan (22) questioned 74 patients (47 men and 27 women) with pernicious anemia about their parents' cause of death. It turned out that 4 fathers and 2 mothers had succumbed to gastric cancer (8%). In a corresponding series of 85 patients with gastric carcinoma, 3 of the parents had died from this disease (3.5%).

while none of the parents of 74 cardiacs had succumbed to gastric carcinoma. The data regarding the causes of death do not seem to have been verified.

Kaufmann & Thiessen (7) examining the relatives of 48 patients with pernicious anemia, found cancer of the stomach in 3 of the parents and in two of the siblings. In their opinion, a hereditary reduction in the gastric acidity might be the cause of gastric carcinoma among the relatives of the parents with pernicious anemia. Their material is, however, of modest size, and they have no control group.

Kaplan & Rigler (6) who recently discussed in detail the relationship between pernicious anemia and gastric carcinoma concluded: »Present evidence, though inadequate, favors the thesis that the two diseases are linked through common hereditary influences.»

Thus, the theory that pernicious anemia and cancer of the stomach are due to common inherited factors is at present supported only by scattered case reports and inadequate systematic studies of the occurrence of these two diseases in the same families.

The author, therefore, attempted to assess the frequency of gastric cancer among the relatives of patients with pernicious anemia, and to compare this frequency with that among the relatives of a corresponding control group of the same sex ratio and age distribution.

Material.

The series comprises 234 patients with pernicious anemia all of whom came from three hospitals in Copenhagen. The diagnosis was verified by the usual criteria, excluding all cases which were doubtful or which lacked sufficient data. The patients correspond with regard to sex and age to previously published analyses, so the author feels justified in considering the series representative.

The control series is made up of 225 healthy persons corresponding to the proband group as regards sex and age.

Comparison of the social distribution of the two groups showed that on the whole the proband group was of a somewhat higher social level, a difference to be mentioned later.

The patients with pernicious anemia and the healthy controls were approached in the same way, and in most cases one or more of the relatives were contacted in order to obtain as full data as possible regarding diseases and causes of death in the family. Parents, siblings and children and in an equal part of the cases in both groups also the parents' siblings were included in the analysis. In the case of the deceased relatives, the causes of death were, if at all possible, confirmed by looking up the death certificates. In all cases of cancer the course of the disease was investigated by correspondence with relatives and hospitals. In numerous instances the writer perused the case records in an endeavour to confirm the diagnosis as far as at all possible. In this way, data were obtained about the diseases and causes of death of about 3,000 relatives in each of the two groups or an average of about 13 relatives for each patient. The two groups of relatives (of the pernicious

anemia patients and the controls) were uniform with regard to sex and age. The manner of confirming cancer was the same in both series: In both groups one-third of the cancer cases was verified by death certificates, one-quarter during a stay in hospital, one-quarter by autopsy, and only about one-tenth is based exclusively on statements from the family.

Accordingly, it appears justified to use these two series in investigating whether the frequency of cancer is higher among the pernicious anemia relatives than among the control series.

Results.

The occurrence of gastric carcinoma among 2,881 relatives of 234 patients with pernicious anemia was compared with the occurrence among 2,956 relatives of 226 controls.

Furthermore, the occurrence of oesophageal cancer as well as of cancer of other sites in both series was investigated.

Table 1.

Cancer of the stomach, oesophagus and other sites among the relatives of patients with pernicious anemia and the relatives of the controls.

	Cancer of the stomach	Cancer of the oesophagus	Cancer of other sites
Pernicious anemia relatives (2,881 persons)	108	16	147
Control series (2,956 persons)	33	11	123

It is evident from table 1 that cancer of the stomach was the cause of death in 108 relatives as compared with 33 cases among the controls. Cancer of the oesophagus and other sites was also more common in the pernicious anemia series, but the difference between the groups is far less marked.

In both series the cases of cancer were evenly distributed among the various categories of relatives, with a uniform sex and age distribution. It therefore seems justified to consider the different groups of relatives in both series together in the following.

The excess mortality from gastric cancer among the pernicious anemia relatives was submitted to a further analysis by comparing the frequency of cancer in this series with the deaths from cancer which might be expected from the mortality in the general population (1931 to 1940).¹

Table 2 compares the total number of cases of cancer in females and males among the pernicious anemia relatives with that in the control series, as well as with the deaths from cancer expected from the mortality in the general population.

This comparison confirms that deaths from gastric cancer are more frequent among the pernicious anemia relatives than might be expected from the mortality

¹ The statistical calculations are due to M. Nyholm, actuary, »Statistica», Copenhagen.

Table 2.

Comparison of the actual number of cases of cancer occurring in the control series of relatives, and in the pernicious anemia series, with the number computed on the basis of the mortality in the general Danish population 1931-40.

Control series.

M a l e s				
	Cancer of the stomach	Cancer of the oesophagus	Cancer of other sites	Total
Actual number	22	8	46	76
Computed number	41.7	6.7	58.4	106.8
F e m a l e s				
Actual number	11	3	77	91
Computed number	33.5	3.1	87.0	123.5

Pernicious anemia series.

M a l e s				
	Cancer of the stomach	Cancer of the oesophagus	Cancer of other sites	Total
Actual number	55	13	52	120
Computed number	38.8	6.3	54.6	99.7
F e m a l e s				
Actual number	53	3	95	151
Computed number	41.0	3.8	103.6	148.4

in the general population, whereas in the control series they were fewer. Both deviations from the computed mortality are significant.

Taken as a whole, this analysis shows a significantly higher mortality from cancer of the stomach among the relatives of patients with pernicious anemia than that found in the general Danish population (1931-40). When the pernicious anemia relatives are compared with the control series, the preponderance of gastric cancer becomes even more marked — but the control series showed a frequency of cancer of the stomach, as well as of other sites, somewhat lower than might be expected from the mortality in the general population.

It is not possible to demonstrate any definite cause of the discrepancy between the incidence of cancer in the control series and the computed cancer mortality. It is reasonable to assume, however, that the control series — collected and ana-

lysed in exactly the same way as the pernicious anemia series — affords a more adequate basis of comparison than the figures taken from the mortality statistics.

Whatever the relationship between the values in the control series and in the mortality statistics, the results indicate that the mortality from gastric carcinoma is higher among the relatives of patients with pernicious anemia.

The pernicious anemia and the control series were equivalent with respect to number, sex, and age. The slight social difference (a somewhat higher social level in the pernicious anemia material) does not explain the increased cancer mortality. Urban and rural populations are approximately equally represented in both materials.

As no exogenous causes of the numerous cases of gastric carcinoma were found in the pernicious anemia material, endogenous factors must be considered.

Recent reports appear to indicate the etiological significance of heredity in stomach cancer (19).

The present evidence makes it reasonable to explain the excess mortality from gastric cancer among the relatives of patients with pernicious anemia, as well as among the patients themselves as a hereditary phenomenon, due to a common predisposition to both pernicious anemia and stomach cancer. There is a constitutional defect of the gastric mucosa in these persons causing achlorhydria and reduced resistance. The nature and intensity of the exogenous actions to which the predisposed individuals are exposed probably decide whether they develop pernicious anemia, gastric carcinoma or both.

Summary.

An excess mortality from gastric cancer among patients with pernicious anemia has previously been shown, but its cause has not been ascertained. In an attempt to further elucidate this question, the occurrence of gastric cancer in the relatives of 234 patients with pernicious anemia was compared with that in the relatives of 226 controls of the same sex and age distribution. The mortality from gastric carcinoma proved to be significantly higher for the pernicious anemia relatives than for the controls, whereas the incidence of cancer of other sites did not differ significantly in the two series.

The control group included less cases of cancer than computed from the mortality statistics. But even a comparison between the incidence of stomach cancer among the relatives of the pernicious anemia group and the number of cancer cases computed to occur in the same, showed a significantly higher incidence of stomach cancer among the pernicious anemia relatives.

The two groups were uniform with respect to number, sex, age, and geographical distribution. Inherited factors play an important rôle in the etiology of pernicious anemia and possibly also of gastric carcinoma. It therefore seems reasonable to assume that the excess mortality from gastric carcinoma in patients with pernicious anemia, as well as among their relatives, may be genotypic, depending on a common inherited predisposition to the two diseases.

Literature.

1. Guiss, L. W. & F. W. Stewart: *Arch. Surg.* 46: 823, 1943. — 2. Hirschfeld, H.: *Ztschr. Krebsforsch.* 11: 376, 1912. — 3. Jorgensen, J.: *Acta med. scandinav.* 139: 472, 1951. — 4. Kade, H.: *Die Bedeutung der chronischen Gastritis als präcarcinomatöse Erkrankung.* Hamburg, 1949. Pp. 120; p. 22 ff. — 5. Kaplan, H. S. & L. G. Rigler: *Am. J. M. Sc.* 209: 339, 1945. — 6. Kaplan, H. S. & L. G. Rigler: *J. Lab. & Clin. Med.* 32: 644, 1947. — 7. Kaufmann, O. & K. Thiessen: *Ztschr. klin. Med.* 136: 474, 1939. — 8. Konjetzny, G. E.: *Der Magenkrebs.* Stuttgart, 1938. Pp. 289; p. 21 ff. — 9. Magnus, H. A.: *Gastritis.* In: Jones, F. A.: *Modern trends in gastroenterology.* London, 1952. P. 323 ff. — 10. Meulengracht, E.: *Report Dansk Selsk. Intern Medicin Nov. 1937.* *Nord. med.* 1: 11, 1939. *Am. J. M. Sc.* 197: 201, 1939. — 11. Mosbech, J. & Aa. Videbæk: *Brit. M. J.* 1950. (I): p. 390. *Ugesk. læger* 112: 985, 1950. — 12. Mosbech, J.: *Heredity in Pernicious Anemia. A Proband Study of the Heredity and the Relationship to Cancer of the Stomach.* Copenhagen, 1953. Pp. 107; p. 45 ff. — 13. Quinke (1876): Quoted after Doebling, P. C. & G. B. Eusterman. *Arch. Surg.* 45: 554, 1942. — 14. Saltzmann, F.: *Acta med. scandinav.* 75: 198, 1931. — 15. State, D., D. Gavisser, Th. B. Hubbard & O. H. Wangensteen: *J. Nat. Cancer Inst.* 10: 433, 1949. — 16. Strandell, B.: *Acta med. scandinav. Suppl. vol. 40.* Stockholm 1931. Pp. 124; p. 96 ff. — 17. Torgersen, J.: *Acta radiol.* 25: 845, 1944. — 18. Waldenström, J.: *Nord. med.* 25: 729, 1945. — 19. Videbæk, Aa. & J. Mosbech: *The Etiology of Stomach Cancer. Acta medica scandinavica* (in print). — 20. Wilkinson, J. F.: *Acta med. scandinav.* 80: 466, 1933. — 21. Zadek, J.: *Klin. Wchnschr.* 54: 1253, 1917. — 22. Zancan, B.: *Minerva med.* 28: 654, 1937.
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Verabreichung von Testosteron propionat bei Asthma bronchiale.¹

(2. Mitteilung.)

Von

HANS ARNOLDSSON und UDO PIPKORN.

(Bei der Redaktion am 16. Oktober eingegangen.)

Elektrophoretische Untersuchungen.

In Fortführung der Untersuchungen mit Testosteron propionat bei Asthma bronchiale Kranken haben wir im folgenden unsere Aufmerksamkeit ausschliesslich dem Verhalten der Serumeiweissfraktionen gewidmet und haben uns des Elektrophoreseverfahrens mit der Tiseliusapparatur bedient.²

Als Pufferlösung diente der Phosphatpuffer, bestehend aus $0.032 \text{ Mol Na}_2\text{HPO}_4 + 0.004 \text{ Mol NaH}_2\text{PO}_4 + 0.0015 \text{ Mol NaCl}$. Die unter dieser Bedingung zu erhaltenden Serumeiweissnormalwerte sind: Albumin 58.2 ± 5 , Totalglobulin 41.8 ± 5 , α Globulin 7.2 ± 3.2 , β Globulin 14.5 ± 3.2 , und γ Globulin 20.1 ± 4.2 .

Das für die vorstehende Untersuchungsserie zur Verfügung stehende Krankengut bestand aus 16 weiblichen Asthma bronchiale Kranken im Alter von 49 bis 66 Jahren. Sämtliche 16 Patienten hatten negative Hautteste. Anamnestisch war ausser den für die Krankheit geläufigen Daten nichts Besonderes zu eruieren, insbesondere nichts, was grundsätzlich unterschiedlich für den einen oder anderen Patienten gewesen wäre. In 7 Fällen lag eine Blutdruckerhöhung über 180 mm Hg systolisch vor.

Die Serumeiweissuntersuchungen wurden sämtlich während einer akuten Asthmaperiode vorgenommen. Das Resultat findet sich in der Tabelle I dargestellt.

Abzulesen ist eine Veränderung der Eiweissfraktionswerte, dessen Gesamtbild wir aufgrund der häufigen gleichmässigen Konstellation mit Vorbehalt als »Synd-

¹ Als Vortrag gehalten beim 2. europäischen Allergiekongress am 21.—23. Mai 1953 in Kopenhagen.

² Die Untersuchungen wurden an dem medizinisch-chemischen Institut der medizinischen Hochschule in Göteborg (Prof. Mellander) durchgeführt, wofür wir hier nochmals unsern herzlichen Dank sagen wollen.

Tabell I.

Veränderungen der Serumeiweissfraktionen bei 16 Asthma bronchiale Kranken.

Totalanzahl Fälle	Albumine (58.2 ± 5)		Totalglob. (41.8 ± 5)		α-Glob. (7.2 ± 2)		β-Glob. (14.5 ± 3.2)		γ-Glob. (20.1 ± 4.2)	
	erhöht	erniedr.	erhöht	erniedr.	erhöht	erniedr.	erhöht	erniedr.	erhöht	erniedr.
16.....	0	15	15	0	11	1	9	2	3	2

rom» ansprechen möchten, und das sich wie leicht zu erkennen ist, aus Albuminverminderung, α- und β-Globulinvermehrung zusammensetzt. In den γ-Globulinen liess sich ausser in 2 Fällen mit Erhöhung keine signifikativen Abweichungen nachweisen. Dieses Ergebnis deckt sich im wesentlichen mit dem von Shedlowsky & Scudder. In 9 von den 16 Fällen, fand sich diese Veränderung.

Zeichnen sich nun die Fälle mit dem »Serumeiweissyndrom« durch irgend etwas gegenüber denen ohne das Syndrom aus? Durch Lebensalter, Dauer der Erkrankung, infektiöse Genese usw? Haben die 9 Fälle evtl. untereinander gemeinsame klinisch-pathologische Züge ausser ihrer Asthmaerkrankung? Oder lassen sich Beziehungen erkennen zwischen den Serumeiweissveränderungen und der Hypertonie?

Alle diese Fragen können wir anhand dieses gewiss kleinen Materials nur negativ beantworten. Auch eine nur annähernd tragfähige Relation zwischen der α-Globulinvermehrung und der in den jeweiligen Fällen vorhandenen Blutdrucksteigerung, lässt sich, so sehr man sie verständlicherweise vermuten möchte, nachdem das Hypertensinogen einschlägigen Arbeiten zufolge (10) an die α-Globulinfraction gebunden sein soll, nicht erkennen. Die Hypertoniefälle verteilen sich etwa gleichmässig auf das Gesamtmaterial und konzentrieren sich nicht auf die 9 »Syndrom-fälle«.

Und so spitzt es sich zu der bangen Frage nach der Bedeutung dieser quantitativ-qualitativen Serumeiweissveränderungen zu. Lassen sich aus ihnen irgendwelche Gesichtspunkte für das Asthma ableiten?

Es liegt in der Natur der Sache, dass die Antwort weder kurz ja noch strikt nein lauten kann. Dagegen möge die Aufmerksamkeit doch auf ein paar Fakta im Zusammenhang mit den Eiweissveränderungen gelenkt sein. Bekanntlich findet sich der Organismus mit einer stärkeren Hypalbuminämie am schwersten ab. Sie bedeutet für das Herz eine Mehrarbeit in doppelter Hinsicht. Die Zirkulation muss infolge des mit dem Absinken der Albumine verbundenen Wasserverlustes mit einem geringeren Blutvolumen ausgeführt oder aufrecht erhalten werden. Zum anderen besitzt das Plasma bei Hypalbuminämie eine erhöhte Viskosität. Beides Umstände, die für das komplexe Geschehen des Asthma bronchiale, insbesondere für die so häufig zu beobachtende und therapeutisch so wenig zugängliche kardinale Komponente, Aufmerksamkeit erfordert. Weiterhin ist auch daran zu denken, dass die Herzglykoside an die Albuminfraction gebunden werden.

Und im Rahmen der α- und β-Globuline interessiert bei den vorläufig noch so sparsamen Kenntnissen auf diesem Gebiet vorerst die bereits erwähnte Tatsache

Interesse, das dass Hypertensinogen an die α -Fraktion gebunden ist. Relationen zur Blutdrucksteigerung bei Asthmatikern, die aus diesem Material nicht hervorgehen, müssten natürlich an einer weit grösseren Anzahl Patienten nachgeprüft werden.

Die β -Fraktion scheint diejenige zu sein, an die die Hormone gebunden sind und in der es auch gelingen zu sein scheint, das Östrogen nachzuweisen. Welche Bedeutung dieser Tatsache für das Asthmagesehen zukommt, ist vorläufig noch nicht abzusehen.

Ein paar Fingerzeige haben sich so immerhin bei der Durchsicht der einzelnen Veränderungen ergeben, aber auch eben nicht mehr.

Eine Überraschung erlebt man nun, wenn man versucht das hier gefundene »Eiweissyndrom« in Vergleich zu setzen zu andernorts elektrophoretisch gefundenen Serumeiweissveränderungen bei verschiedenen Erkrankungen oder Krankheitseinheiten. Da ist es tatsächlich ausser der normalen und pathologischen Schwangerschaft (1, 10, 17) der Diabetes mellitus, der die gleichen Abweichungen im Serumeiweisspanorama aufzeigt. Ausgerechnet der Diabetes mellitus, der sowohl nach älteren und auch wieder neueren Arbeiten (6, 7, 8, 9, 18, 19) zumindest sehr selten gleichzeitig mit dem Asthma bronchiale zusammentrifft.

Ebenso wird manch einen in Erstaunen setzen, dass sich zu dem elektrophoretischen Eiweissbild der Nebennierenunterfunktion (2) und auch zu dem der bekannten hyposphärpathologischen Zustände keine Brücke schlagen lässt. Für die ersteren wurde bekanntlich von einigen Autoren eine starke γ -Globulinvermehrung und für die letzteren normale β -Globulinwerte gefunden.

Testosteron und Serumeiweissbild.

An 12 von den 16 Patienten wurde im Anschluss daran Elektrophoreseuntersuchungen im Verlauf einer Testosteronbehandlung, 10 mg täglich 10 Tage lang durchgeführt und zwar ausser vor Einsetzen der Behandlung nach der 4. und nach der 9. Injektion.

Das Ergebnis ist in der Tabelle II zusammengestellt und gestaltet sich zusammengefasst folgendermassen: In der Albuminfraktion kam es in 6 Fällen zu einem Anstieg der erniedrigten Werte, in 3 Fällen zu einem weiteren Absinken. Diese 6 Fälle wiesen im Zustandsbild ihres Asthmas unter der Hormonbehandlung eine Verbesserung auf, ob die jedoch dem Hormon zugute gerechnet werden darf, kann nicht entschieden werden. Dann sind drei Fälle, bei denen es unter der Testosteronzufuhr zu einem weiteren Absinken des bereits erniedrigten Serumalbumins kam. Sie gehören im übrigen zu denen, die bereits im ersten Teil dieser Arbeit (Acta med. scand. Vol. CXIII, 1952) Erwähnung fanden, und die nach jeder Testosteroninjektion über zunehmende einige Stunden anhaltende Schwere in der Brust klagten. Wie weit hier Zusammenhänge zwischen dem Eiweisspiegel und dem psychischen Phänomen vermutet werden können, ist natürlich nicht zu übersehen. Bei diesen Patienten kam es zu keiner wesentlichen Verbesserung ihres Asthmas.

In der α -Globulinfraktion konnte 5 Mal ein Absinken der erhöhten Werte re-

Tabell II.

Veränderungen der Serumeiweissfraktionen nach Testosteronzufuhr 10 mg täglich bei 12 Asthma bronchiale Kranken.

Signatur		Albumine (58.2 \pm 5)	Totalglob. (41.8 \pm 5)	α -Glob. (7.2 \pm 2)	β -Glob. (14.5 \pm 3.2)	γ -Glob. (20.1 \pm 4.2)
2	v.	40	60	11	26.5	22.6
	4.	54	46	26.5		19.5
	9.	51	48.5	13.5	17	18.0
5	v.	48.5	51.5	9.8	17.2	24.5
	4.	49.1	50.9	9.3	17.3	24.3
	9.	—	—	—	—	—
6	v.	33.5	66.5	15	20.5	31
	4.	34.7	65.3	11.1	19.5	34.7
	9.	34	66	13.6	19.4	33
7	v.	46.4	53.6	17	22.3	14.3
	4.	53	47	9.9	19.7	17.4
	9.	49.6	50.4	13.7	19.7	17
8	v.	44	56	14	21	21
	4.	35	65	17	22.5	25.5
	9.	40	60	14	17.5	23.5
9	v.	45	55	15	18	22
	4.	52	48	11	14	23
	9.	48	52	9	22.5	20.5
10	v.	45	55	10.5	15	29.5
	4.	42.5	57.5	10.5	17	30
	9.	38	62	15	18	29
11	v.	43.5	56.5	15.5	15.5	29.5
	4.	44.5	55.5	13.5	19.5	22.5
	9.	52	48	12	19	17.5
12	v.	41	59	9.5	17	32.5
	4.	46.5	53.5	8.5	16.5	29.5
	9.	53.5	46.5	7.5	16.5	22.5
13	v.	48.5	51.5	17	11	23.5
	4.	51.5	48.5	12.5	12	24
	9.	—	—	—	—	—
14	v.	51.5	48.5	—	29.5	19
	4.	44.5	55.5	13	19	23.2
	9.	43	57.5	15.5	20.8	20.8
15	v.	46.4	53.6	8.8	24.9	19.9
	4.	48.5	51.5	14.6	21.5	15.4
	9.	51.9	48.1	10.1	23.4	14.6

gistriert werden, davon jedoch nur 2 Mal bis zur Norm. In zwei der fünf Fälle war der Abfall kontinuierlich, in 3 Fällen waren die α -Globulinwerte bei der Elektrophoreseuntersuchung nach der neunten Testosteroninjektion gegenüber dem Wert nach der vierten Injektion wieder angestiegen. In 3 Fällen stiegen die an und für

sich bereits erhöhten α -Globulinwerte noch weiterhin an. Nur in zwei Fällen ging der Abfall der α -Globulinwerte mit einem Anstieg der Albuminfraktion einher. Letzteres würde keine direkte Bestätigung der von amerikanischer Seite (4, 5, 11) ausgesprochenen Annahme einer festen Koppelung der Albumine und α -Globuline, Absinken des einen mit obligatorischem Ansteigen des anderen, bedeuten. Dabei ist allerdings zu berücksichtigen, dass hier keine normalen Verhältnisse vorlagen.

Und die erhöhten β -Globulinwerte sanken in 3 Fällen ab und stiegen in einem Fall weiterhin an. In zwei von den drei Fällen ging der Abfall parallel mit dem Absinken der α -Globuline und dem Anstieg des Albumins. In 2 Fällen waren die Reaktionsverläufe genau entgegengesetzt, d. h. Abfall des einen und Anstieg des anderen.

Überblickt man das Ergebnis jetzt, so ist in einem gewissen Prozentsatz der Fälle eine Normalisierungstendenz der pathologischen Serumeiweisswerte unter Testosteroninjektionen unverkennbar. Ob diese allerdings gefolgt ist von einer Änderung im Krankheitsgeschehen, kann anhand dieser Ergebnisse wohl vermutet, nicht aber mit Sicherheit gesagt werden. Dass hier auch Dosierungsfragen wieder mit hineinspielen, ist möglich und bleibt, wie die Reihe anderer angerissener Fragestellungen weiter abzuklären.

Summary.

At sixteen patients between the ages of 49 and 66 suffering from asthma bronchiale were performed elektrophoretic studies of plasma proteins. In nine cases were obtained significant changes in the proteins consisting in decrease of albumin and increase in the α - and β -globulins. The authors apply the term »plasma protein syndrome« with reservation for all the changes and believe that the »syndrome« is characteristic for the asthma bronchiale. Then testosterone-propionate 10 mg a day for 10 days was given to twelve of the sixteen patients. The albumin increased in 5 cases, the pathological α -globulins decreased in 5, but only in two cases to normal values, and the β -globulins decreased in three cases. Sure relations between the tendency to normalisation of the plasma protein fractions and the clinical symptoms were not observed, yet three cases showed an impairment of the asthma, when the albumin fraction decreased furthermore under testosterone treatment.

Literaturverzeichnis.

1. Bleek: Zit. nach K. Stürmer: Die quantitative Elektrophorese in der Medizin, Springer-Verlag Berlin, Göttingen, Heidelberg 1952. — 2. Mc Cullagh, E. P. & Lewis, L. A.: J. Clin. Endocrinol. 7, 559, 1947. — 3. Mc Cullagh, E. P., Lewis, L. A., & Owen, B. J.: Cleveland. Clin. Quart. 10, 88, 1943. — 4. Chow, B. F., Allison, I. B., Cole, W. H. & Seeley, R. D.: Ann. N. Y. Acad. Sci. 47, 297, 1946. — 5. Chow, B. F., Seeley, R. D., Allison, I. B., & Cole, W. H.: Arch. of Biochem. 10, 69, 1948. — 6. Gutmann, M. J.: Int. Arch. of Allergy a. appl. Immunology 4, 118, 1953. — 7. Joslin, E. P. a. o.: The treatment of diabetes mellitus, 8 thnd, Philadelphia 1946. — 8. Kern, R. A.: Trans. Ass. Amer.

Phys. 49, 23, 1934. — 9. Koenig, F.: Med. Klin. 31, 546, 1935. — 10. Lagerkrantz, C.: Uppsala läkareförening Förh. 51, 1945/46. — 11. Lewin, M. H.: Amer. J. Physiol. 138, 258, 1943. — 12. Lewin, M. H. & Leatham, A.: Amer. J. Physiol. 136, 306, 1942. — 13. Moore, D. H., Lewin, M. H. & Leatham, A.: J. of Biol. Chem. 153, 349, 1944. — 14. Plentl, A. A., Page, I. H. & Davis, W. W.: J. of Biol. Chem. 147, 143, 1943. — 15. Schneider, R. W. & McCullagh, E. P.: J. Clin. Endocrinol. 4, 535, 1944. — 16. Shedlowsky, S. & Scudder, Y.: J. exper. Med. (Am.) 75, 119, 1942. — 17. Stürmer, K.: Z. exp. Med. 117, 359, 1951. — 18. Swern, N.: J. of Allergy 1, 375, 1931. — 19. van Ufford, Qu.: Int. Arch. of Allergy a. appl. Immunology 3, 234, 1952.

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Cushing's Syndrome Associated with Obliterative Arterial Disease and Multiple Subcutaneous Nodules (Ehlers-Danlos Syndrome?).

By

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(Submitted for publication October 20, 1953.)

The clinical aspects of Cushing's syndrome (C. s.) with its physical and physiological changes are well known, and pathological mental changes associated with this syndrome are described by many investigators. Bleuler (1) and Stoll (8) have stressed that there is a certain correspondence between »the endocrine psychosyndrome» and »the local cerebral syndrome», further that each endocrine disease has no special psychopathology (the latter being the same in both hyper- and hypofunction — for instance in C. s. and in Addison's disease).

Relatively few descriptions of the Ehlers-Danlos syndrome (E.-D. s.) have been published, most of them from the U. S. A. The E.-D. s., consisting of a well defined clinical entity (hyperelasticity and fragility of the skin and blood vessels, hypermobility of the joints, pseudotumours over bony prominences and *movable subcutaneous nodules*) is perhaps more frequent than hitherto observed. In 1912 Shaw and Hopkins (7) reported a patient with the E.-D. s. and hard subcutaneous nodules and in 1934 Tobias (10) gave a report of the E.-D. s. associated with small, firm, non-tender, subcutaneous nodules. A description of the characteristic subcutaneous nodules has not to my knowledge been published in the Scandinavian literature. American authors describe those nodules as a very important sign of the disease, being of particular importance to radiologists. In X-ray appearance calcified hæmangiomatous phleboliths may resemble the calcified E.-D. nodules, but the phleboliths show more variation in size, are apt to be distributed throughout the deeper soft tissue and contain multiple concentric strata of calcium. The characteristic feature of the E.-D. nodules will be described later on in connection with our case.

From Scandinavia there are few reports of the E.-D. s., none of them to my knowledge with descriptions of the typical nodules. Wigers (12) has presented

2 cases with articular hyperextensibility, cutaneous hyperelasticity and vascular fragility. Husebye (3) has given a report of 8 cases occurring in the same family. Further cases are described by Kornstad (5).

Few descriptions in the literature deal with a possible connection between the Ehlers-Danlos syndrome and endocrine diseases. Strandberg (9) and Johnsen & Falls (4) have suggested such a connection.

In the women's department, Gaustad Mental Hospital, we have observed a patient with a typical Cushing's syndrome associated with the Ehlers-Danlos syndrome. The question arises whether there is a close connection between the two syndromes or whether they only are the outcome of two different diseases.

Case report: Woman, aged 52. Her illness seems to have commenced 1914, at the age of 44. From that time marked facial hirsutism appeared. Two years later she was admitted to a mental hospital where periods of agitation and confusion occurred, the periods interrupted by electroconvulsive treatment. After discharge (22 months from admittance) she remained psychologically healthy until 1952. On July 11 she was admitted to Gaustad Mental Hospital with a typical Cushing's syndrome (obesity, changes of the skin, fuzzy hair, a «moon-shaped» face, slight exophthalmos, acrocyanosis, muscular weakness and fatigability and loss of libido). During the course of her hospitalisation four periods of agitation, with complete confusion occurred. Each period followed psychic stress (fear of operation) and each *psychotic period was brought to an end by electroconvulsive treatment*. A correlation between the fasting eosinophile count and the occurrence, exacerbation and remission of mental derangement was observed. (A closer description of the psychiatric and somatic aspects of the patient's disease was published in «Tidsskrift for Den Norske Lægeforening», 1953 (6).)

The patient had also a *very marked obliterative arterial disease of the legs and forearms*. Further she had *hard, moveable subcutaneous nodules on all four extremities*, most numerous on the extensor surfaces. X-ray pictures showed disseminated, small, rounded, calcareous nodules lying immediately under the skin. A central zone of relatively increased radio-luency is surrounded by a ring-like shadow. (Fig. 1.) 3 nodules were taken for microscopic and chemical investigation. The microscopic description of a typical subcutaneous nodule was as follows: (Fig. 2).

«The formalin-fixed specimen was a rather firm, ovoid node measuring 3 by 4 mm, surrounded by scanty fat tissue. The surface was smooth. Sectioning showed a thin fibrous capsule covering amorphous masses of necrotic fatty tissue with occasional calcified areas. The cellular reaction was inconspicuous. Frozen sections revealed moderate amounts of double refracting substances especially beneath the capsule. A few capsular arterioles were slightly sclerotic (diffuse hyperplastic sclerosis). There were no signs of malignancy nor of specific inflammation. Diagnosis: Fat necrosis (encapsulated).» Prof. O. Torgersen.

The origin of those nodules was thoroughly discussed and diagnoses as phleboliths, necrobiosis lipoidica diabetorum and calcinosis universalis were excluded.

The microscopic section of the nodules in our case is «identical» with the findings described with the Ehlers-Danlos syndrome by Holt (2). In our case there is perhaps some hyperelasticity of the skin of the arms, especially round the elbows. There is also some fragility of the skin and blood vessels, moreover some hypermobility of the joints, but none of these signs were very pronounced. In 1916 and 1952 she had been operated upon, respectively for a «tumour» over os sacrum and for one just below the right patella. Most likely these «tumours» were molluscoid pseudotumours known to be characteristic of the E.-D. s.

In our patient the left adrenal gland was found to be hyperplastic and a total adrenalectomy was performed January 29, 1953. The 17-ketosteroid excretion fell from 11.8 mg in 24 hours (corr.) before, to 9.5 mg after the operation. Periods with agitation and confusion again occurred, again terminated by electroconvulsive treatment. *Psychologically there was very little or no change after the operation.* Somatic changes were observed. Before the operation she had to shave 3 times a week; afterwards she was content with one or two shaves a week. The loss of hair on the head was less marked. There was some loss of weight. The blood pressure was unchanged.

A closer investigation of the family history revealed that a sister of the patient, aged 44, was suffering from a mild form of C. s. (moon-shaped face, hirsutism and slight obesity), but no signs of the E.-D. s. (especially no subcutaneous nodules) were found by X-ray. Her brother and a son of his were also examined clinically and by X-ray without finding of nodules. No familial anomalies were found except short fingers in the case of our patient, her sister, brother and her father.

Other investigators are encouraged to look for subcutaneous nodules in patients with C. s., especially if the condition is of long duration and accompanied by psychosis. Each case with the E.-D. s. ought to undergo X-ray examination for subcutaneous nodules.

Summary.

A case with a typical Cushing's syndrome in a woman, aged 52, is described, in whom clinical and X-ray examination revealed subcutaneous nodules which correspond to the characteristic findings in the Ehlers-Danlos syndrome (described by John F. Holt in 1946). Some other signs of the E.-D. s. were found (pseudotumours and fragility of the skin and blood vessels). The question arises whether there is a close connection between the two syndromes or whether they only are the outcome of two different diseases. (A possible connection between the E.-D. s. and endocrine diseases has been suggested by J. Strandberg and by Johnson & Falls).

Literature.

1. Bleuler, M.: Schweiz. Med. Wochenschr. 22: 512: 1951. — 2. Holt, John F.: American Journ. of Roent. and Rad. Ther. 55: 420: 1946. — 3. Husebye, K. O.: T. f. N. L. 7: 185: 1952. — 4. Johnson, St. A. M. & Falls, H. F.: Arch. Dermat. & Syph. 60: 82: 1949. — 5. Korstad, L.: Nord. Med. 50: 973: 1953. — 6. Laane, C. L.: T. f. N. L. 17: 665: 1953. — 7. Shaw, H. B. and Hopkins, P.: Proc. Roy. Soc. Med. 6: 20: 1912. — 8. Stoll, W. A.: Die Psychiatrie des Morbus Addison. Sammlung psychiatrischer u. neurol. Einzeldarstellungen. Georg Thieme Verlag. Stuttgart 1953. — 9. Strandberg, J.: Nord. Med. 1: 626: 1939. — 10. Tobias, N.: Arch. dermat. & Syph. 30: 540: 1934. — 11. Weber, F. P.: Urol. & Cutan. Rev. 27: 407: 1923. — 12. Wigers, F.: Nord. Med. 43: 304: 1950.



Fig. 1. Calcified subcutaneous nodules from the forearm of our patient. Distribution is bilaterally symmetrical and largely superficial.

LAANE: Cushing's Syndrome.

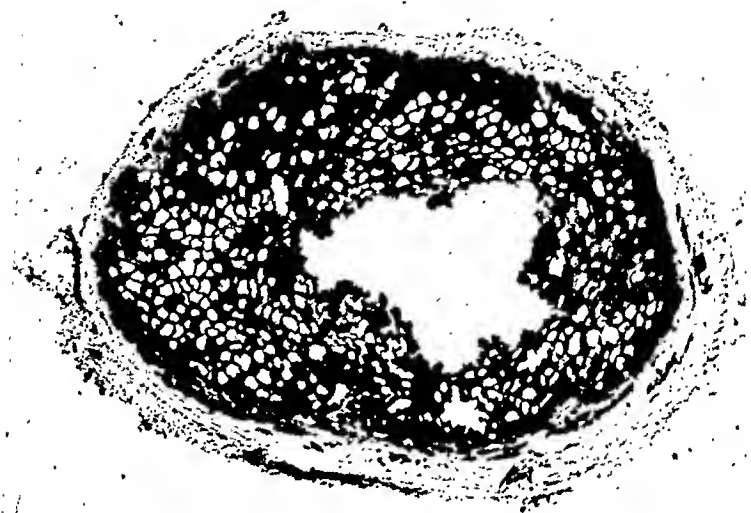


Fig. 2. A typical subcutaneous nodule from our patient. Calcified necrotic fat is surrounded by a thin fibrous capsule.

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On the Pathogenesis of the Dumping-Syndrome.

By

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(Submitted for publication July 7, 1953.)

The term dumping comprises a series of symptoms occurring after subtotal gastrectomy, total gastrectomy or vagotomy.

The symptoms begin in the course of half an hour after a meal with abdominal discomfort (most frequently in the form of epigastric oppression, or rumbling and gurgling in the stomach), nausea, palpitation in conjunction with dizziness and a sensation of heat. In addition the patients feel such a pronounced and troublesome weakness, fatigue and drowsiness that they often have to lie down. After three quarters of an hour to one hour they feel well again. Large meals, whole milk and especially sweets give rise to the most severe attacks.

Besides dumping, these patients often display symptoms of hypoglycaemia (weakness, sleepiness), starting from $1\frac{1}{2}$ to $2\frac{1}{2}$ hours after the meal and subsiding in the course of half an hour. These attacks have been previously termed late dumping attacks, a term which has now fallen out of use.

The present paper deals exclusively with the actual dumping syndrome.

Several papers have been published to elucidate the pathogenesis of this syndrome.

Alvarez (1) has observed typical attacks and, roentgenologically, rapid emptying of the stomach in two neurotics who had not had any stomach operations, and suggests that an especially unstable nervous system might be the most essential aetiological factor.

Butler and Capper (2) provoked the syndrome in 79 patients, partly by distension of the jejunum, partly by torsion of the stomach stump (by placing a mercury-filled bag in the latter). The attacks were most frequent in the erect posture. They could often be checked by a splanchnic block; this was considered indicative of

the symptoms being due to impulses released through the sympathetic nervous system.

Butler and Capper's theory that torsion of the stomach stump is an important pathogenetic factor has been contradicted by Goligher and Riley (5) on the basis of the observation that dumping becomes more frequent when increasingly large portions of the stomach are removed, *i. e.* it will be most frequent after total gastrectomies. They were able to provoke dumping by inflating a balloon placed in the jejunum under roentgenological control.

Machella (7) concluded from his examination of 16 patients that dumping occurs when the jejunum is distended by food which passes rapidly through the anastomosis. As the food is not diluted in the stomach, its hypertonic constituents (*e. g.* dishes made with whole milk) should give the greatest distension by drawing water into the lumen of the intestine.

Schechter and Necheles (10) were unable to find any explanation of the occurrence of the syndrome; they found in particular no connection between the symptoms and distension of the stomach stump and the jejunum with contrast medium.

In contrast with these rather mechanical causes to explain the pathogenesis of the syndrome, Smith (13) has put forward a chemical explanation of the phenomenon. On the basis of experiments made with six patients he showed that a fall in the serum potassium level is the cause of dumping, especially of such symptoms as weakness, fatigue and drowsiness. The fall in the serum potassium level is associated with electrocardiographic and electromyographic signs of hypopotassemia. He has not stated the time when the patient's indisposition reached its maximum, and thus not the serum potassium value at this time. Moreover the author has not stated the normal range of serum potassium values or what he considers to be a significant fall.

The purpose of the present study was to examine the relationship of serum potassium to the symptoms, as it is considered peculiar that the, sometimes small, quantities of sugar (10—15 gm) which may give rise to the attacks should be capable of producing a fall in the serum potassium value.

As patients who have undergone gastrectomy often have an increased maximal blood sugar value and show a pronounced hypoglycaemic phase in peroral glucose tolerance tests (3, 4, 13), an intravenous glucose tolerance test was made in order to arrive at an estimate of the carbohydrate metabolism. This examination also shows whether the malaise may be due to a transitory hypertonia of the blood (*cf.* the discomfort experienced in intravenous injection of a hypertonic sodium thiosulphate solution in renal function tests).

Besides using a hypertonic glucose solution administered by the mouth an attempt was also made to provoke the attacks with hypertonic solutions of magnesium sulphate, sodium chloride and galactose, and with distilled water. This was done in order to find out whether a specific effect can be attributed to glucose, or whether a given substance can produce the symptoms simply by virtue of its volume or its osmotic concentration.

The variations in the serum potassium values during the dumping attacks have been previously studied by the writer (8) in a smaller paper.

Material and Methods.

The following investigations were made in six patients with the dumping syndrome:

(A) Peroral glucose tolerance tests with 70 gm of glucose in a treble isotonic solution. The blood sugar, serum potassium, electrocardiogram, systolic blood pressure and pulse rate were then followed. (Systolic blood pressure and electrocardiogram are lacking in case 2.)

(B) Intravenous glucose tolerance tests according to Stefan Jørgensen's (6) method. 40 ml of a 50 per cent. solution are injected. The blood sugar curve is estimated on the basis of the circumscribed area and the time passing before the blood sugar has fallen to the fasting value. Blood sugar, serum potassium, electrocardiogram, systolic blood pressure and pulse rate were then followed. (This examination was not made in Case 6.)

The potassium level was determined by means of flame-photometry; values from 14 to 20 mg% are within the normal range. Variations under 1—2 mg% cannot be considered significant.

The electrocardiograms reproduced are second limb leads.

Case Records.

Case 1. A man, aged 49, who had had a Billroth II gastric resection in 1944 for duodenal ulcer.

Since that date he became ill from 5 to 10 minutes after the ingestion of sweets, even after such small quantities as 10—15 gm of sugar; during these attacks he had nausea, palpitation, headache with sleepiness and cold sweats, so that he had to lie down for half an hour. A glass of milk and very large meals could produce the attacks, though these were less severe. The malaise was over in the course of an hour. Physical examination showed nothing abnormal. Roentgenological examination of the stomach showed normal emptying.

Case 2. A man, aged 43, who had had a gastroenterostomy and entero-anastomosis for gastric ulcer in 1930, gastric resection (a modified Polya) in 1935, and vagotomy in 1951. Afterwards the patient developed dumping symptoms with epigastric oppression associated with nausea, palpitation, a sensation of weakness and cold sweats, beginning from 10 to 15 minutes after the ingestion of sweets and milk. The attacks subsided when he lay down for an hour. In addition he complained of grumbling pain in the epigastrium. In November, 1951, the entero-anastomosis was closed by operation. His condition remained unchanged after this operation. Apart from tenderness to palpation below the left costal margin the physical examination showed nothing abnormal. Roentgenological examination of the stomach showed normal emptying.

Case 3. A man, aged 29, who had had a Polya gastric resection for duodenal ulcer in 1949. He never felt well after the operation, and his complaints were as follows:

(a) Spontaneous attacks of pain immediately above the right iliac fossa. The pain was characterized as dry and intense, often followed by bilious vomiting and occurring at intervals of two months.

(b) From the autumn of 1951 onwards he had attacks of the following nature: Immediately after meals, especially after hot meals, he developed attacks (worst after oatmeal

porridge) in the form of a sensation of fullness and distension of the abdomen in conjunction with fatigue and sweating, but not with palpitation or actual exhaustion. He felt no appreciable improvement on lying down, but the attacks always subsided in the course of an hour. Apart from hot milk dishes, he had no intolerance to special articles of food. Physical examination showed nothing abnormal. Psychiatric examination failed to explain the presence of the symptoms. Roentgenological examination of the stomach showed normal emptying.

Case 4. A woman, aged 42, who had had a Polya gastric resection for duodenal ulcer in 1948. From the summer of 1950 onwards she developed attacks from 5 to 10 minutes after large meals, which produced the worst attacks, and after sweets in comparatively large quantities (50–100 gm); they began in the form of palpitations, whilst at the same time she became tired and sleepy, with rumbling and gurgling in the stomach, and eructation (the most troublesome of her complaints). She had also occasionally a sensation of grumbling and oppression below the left costal margin. A carminative powder exerted no effect on these attacks. The patient could take 2 or 3 lumps of sugar in a cup of coffee.

Apart from slight tenderness below the left costal margin the physical examination showed nothing abnormal. Roentgenological examination of the stomach showed rapid emptying.

Case 5. A woman, aged 50, who had been subjected to a Polya gastric resection for duodenal ulcer in 1950. Since the operation she suffered constantly from dyspepsia of indefinite nature, with painful epigastric oppression after the meals and frequent, as a rule postprandial, vomiting. Complaints at the time of writing were as follows, 1–5 minutes after most meals, but worst after sandwich-cake and porridge, she developed a feeling of oppression across the epigastrium immediately above the umbilicus, often combined with nausea and vomiting. There were occasional palpitations but never sweating or loss of consciousness. Physical examination showed a very lean woman who was not very communicative but otherwise normal. Roentgenological examination of the stomach showed rapid emptying.

Case 6. A man, aged 34, who had been subjected to a Polya resection for duodenal ulcer in February, 1952. He had not felt well since the operation, for besides constant fatigue he displayed the following symptoms; 5–10 minutes after meals he developed a sensation of heat in the head, nausea and a feeling of apathy, at times also sweating and palpitations. The malaise subsided in the course of an hour, most rapidly when he lay down. The attacks also occurred if he took a meal while lying down. Chocolate, porridge and milk dishes were especially provocative. Physical examination showed nothing abnormal. Roentgenological examination of the stomach showed rapid emptying.

Results.

(A) *Peroral glucose tolerance test.*

Case 1: See Figure 1 and electrocardiograms.

The patient developed nausea and became tired in 2–3 minutes. The malaise reached its maximum in about a quarter of an hour with violent nausea, headache, dizziness and sleepiness. The patient sat hunched up in a chair, looking very distressed. The skin was cool and clammy. His handshake seemed uninfluenced. The gait was normal. He recovered completely in the course of 60 minutes. There were no symptoms of hypoglycaemia.

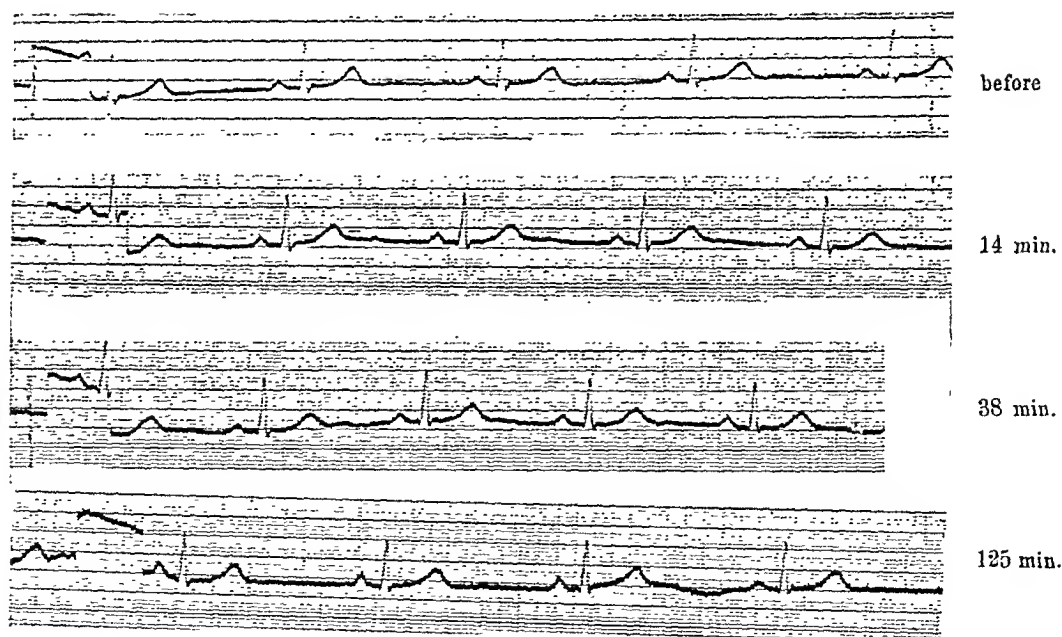
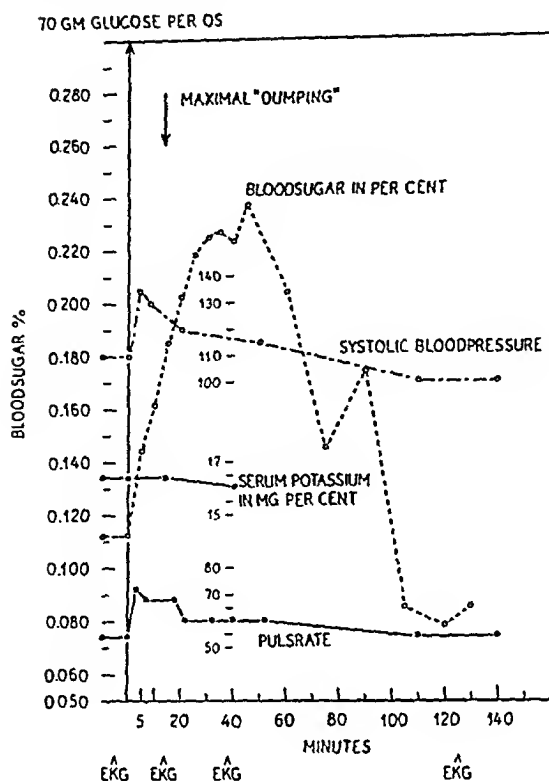


Figure 1. Case 1: Blood sugar (after 70 gm of glucose given by the mouth), serum potassium, systolic blood pressure, pulse rate, and electrocardiograms taken before and during the experiment.

In Figure 1 the arrow shows the time when the malaise reached its maximum. At this time the serum potassium was at the same level as at the beginning of the experiment. Apart from a variation in the frequency an electrocardiogram recorded after 14 minutes showed no definite changes. Blood sugar curve: maximum at 0.237 per cent., otherwise nothing abnormal, on particular no hypoglycaemic phase. Systolic blood pressure and pulse rate reached maximum in 3—5 minutes.

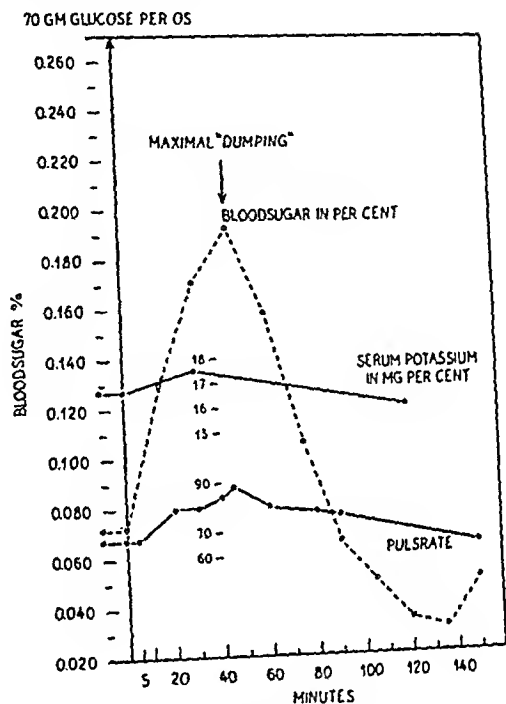


Figure 2. Case 2: Blood sugar (after 70 gm of glucose given by the mouth), serum potassium and pulse rate.

Case 2: See Figure 2. (Electrocardiogram and blood pressure were not recorded in this case.)

After nearly 10 minutes the patient developed rumblings in the stomach, soon followed by nausea and a sensation of weakness. The nausea reached its maximum in 45 minutes, the patient lying down on the floor, complaining of an unbearable nausea and loss of strength in arms and legs. The skin was not clammy or cool in this case. The patient's handshake was considered to be weak. The gait was normal. After 60 minutes the nausea subsided, and the handshake was normal. The languor persisted as the only symptom till the end of the experiment. Cf. the pronounced hypoglycaemic phase.

The arrow in Figure 2 shows the time when the malaise reached its maximum. The serum potassium curve shows that the level can hardly have been lowered at this time. Blood sugar curve: the maximum was 0.193 per cent.; there was a pro-

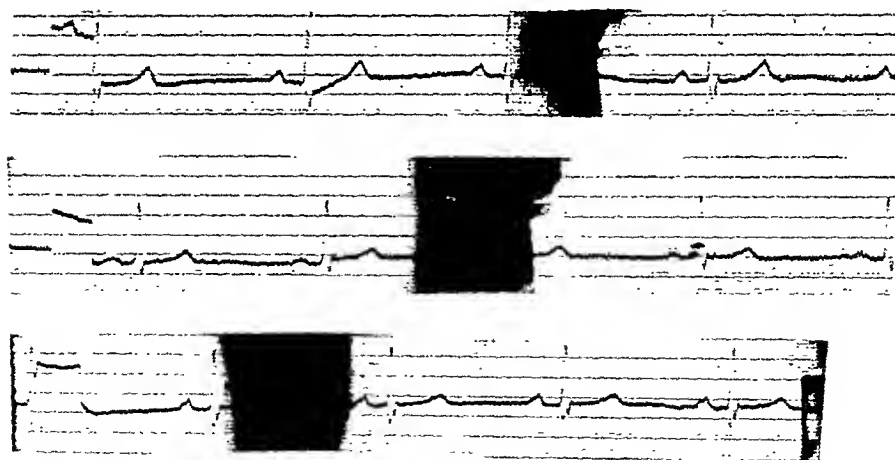
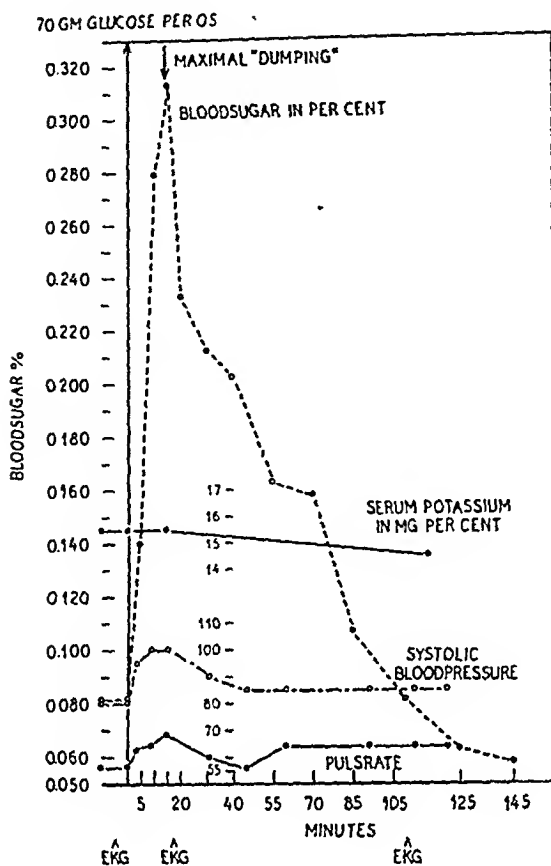


Figure 3. Case 3: Blood sugar (after 70 gm of glucose given by the mouth), serum potassium, systolic blood pressure, pulse rate, and electrocardiograms taken before and during the experiment.

nounced hypoglycaemic phase with its minimum at 0.030 per cent. The pulse rate reached its maximum simultaneously with the maximal malaise.

Case 3: See Figure 3 and electrocardiograms.

The patient developed epigastric oppression, nausea, headache and gurgling in the stomach in the course of 4 minutes. In 9 minutes he felt *fall-in* and sleepy. The malaise reached its maximum in a quarter of an hour, the patient yawning loudly and hunching up in the chair. His gait and handshake were uninfluenced. In the course of an hour the malaise abated. He was influenced to some degree by the hypoglycaemic phase.

The arrow in Figure 3 shows the time when the malaise reached its maximum. At this time the serum potassium was at the same level as before the administration of glucose. Electrocardiograms recorded after 17 and 110 minutes showed a distinct flattening of the T-waves, and changes in frequency. The Q—T interval was unchanged. The sugar curve reached its maximum at 0.313 per cent. in 15 minutes. There was a hypoglycaemic phase. Blood pressure and pulse rate reached maximal values in about 15 minutes.

Case 4: See Figure 4 and electrocardiograms.

Vigorous eructation occurred in 3 minutes. After about 10 minutes the patient felt rumbling and oppression below the left costal margin. A few minutes later, he complained of palpitation, fatigue and a sensation of heaviness in the head; the malaise reached its maximum in about 25 minutes. The patient's gait and handshake were uninfluenced. She felt well again after an hour or so.

The arrow in Figure 4 shows the time when the malaise reached its maximum. At this time the serum potassium was at the same level as before the administration of glucose. In addition to a rise in the frequency the electrocardiogram recorded after 30 minutes showed a flattening of the T waves; the Q—T interval was unchanged. The blood sugar curve showed a maximum of 0.206 per cent. after 70 minutes. There was a hypoglycaemic phase. Pulse rate and blood pressure reached maximum in 10—20 minutes.

Case 5: See Figure 5 and electrocardiograms.

Nausea and a sensation of oppression immediately above the umbilicus began in the course of 2 minutes. This was followed by increasing nausea, pronounced malaise and fatigue. The pulse rate quickened. The patient's gait and handshake were uninfluenced. The symptoms subsided in the course of half an hour, and she felt well again after one hour.

The arrows in Figure 5 indicate the time during which the malaise was most pronounced. The serum potassium curve does not explain the course of the experiment. The electrocardiogram recorded after 29 minutes shows accelerated action, diphasic T waves and slightly depressed S—T intervals. The Q—T curve was unchanged. The electrocardiographic changes became normal after 102 minutes. The blood sugar curve reached its maximum at 0.389 per cent. after 40 minutes. The blood pressure showed a slight rise only, and the pulse rate reached its maximum in 20—25 minutes.

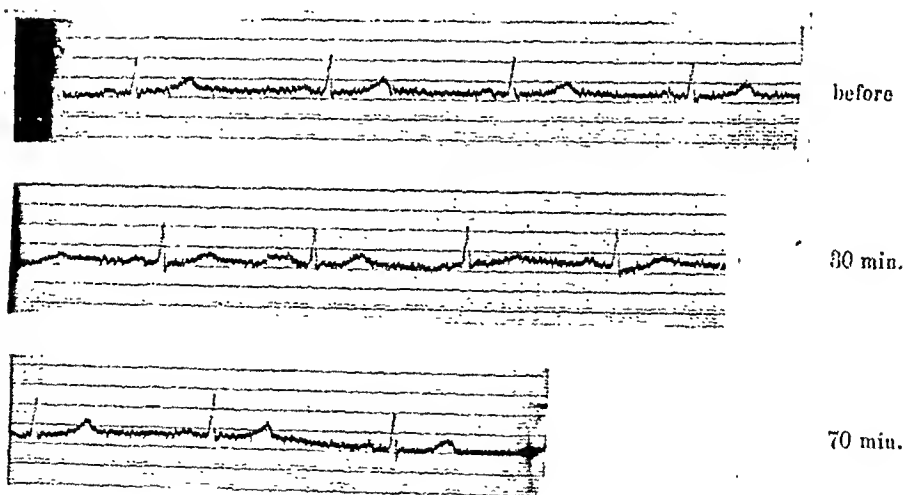
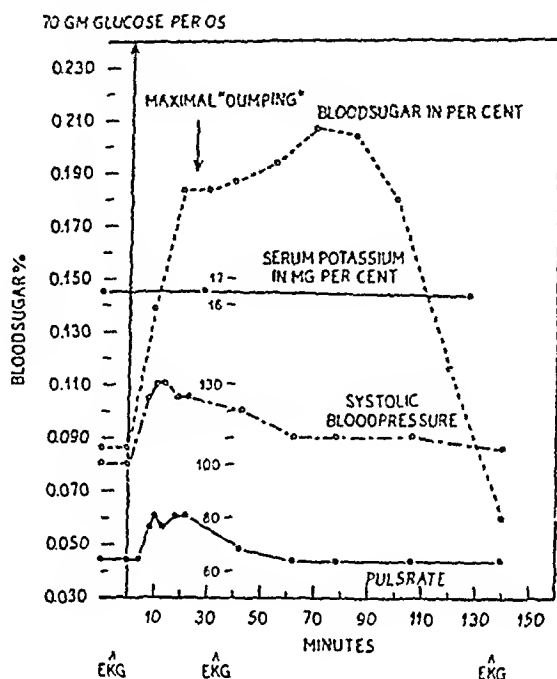


Figure 4. Case 4: Blood sugar (after 70 gm of glucose given by the mouth), serum potassium, systolic blood pressure, pulse rate, and electrocardiograms taken before and during the experiment.

Case 6: See Figure 6 and electrocardiograms.

The patient developed a feeling of nausea and oppression, and rumbling in the abdomen, and profuse sweating in 2 minutes. After 5 minutes he had pronounced palpitation and felt tired and faint. He was very sick, looked distressed and sat hunched up in the chair. The malaise remained unchanged for about 30 minutes. After about 80 minutes he felt well again. He was only slightly influenced by the hypoglycaemic phase.

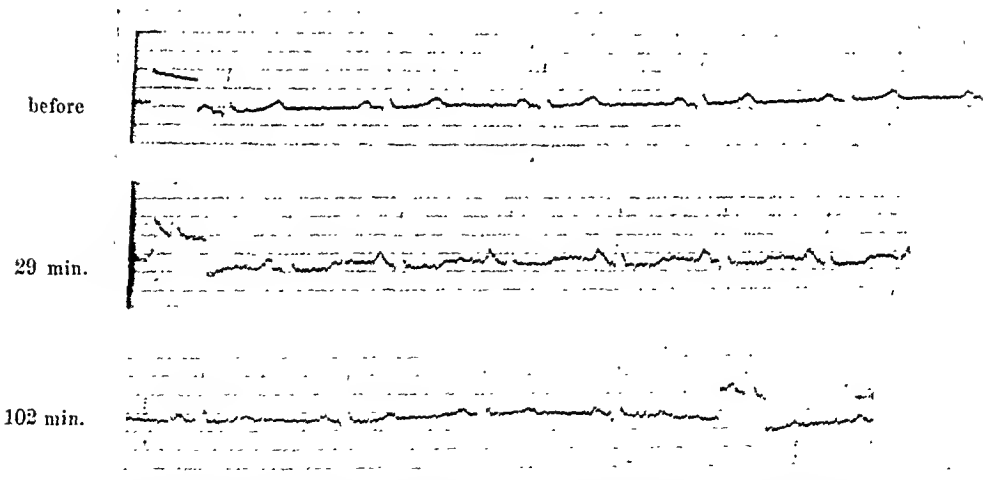
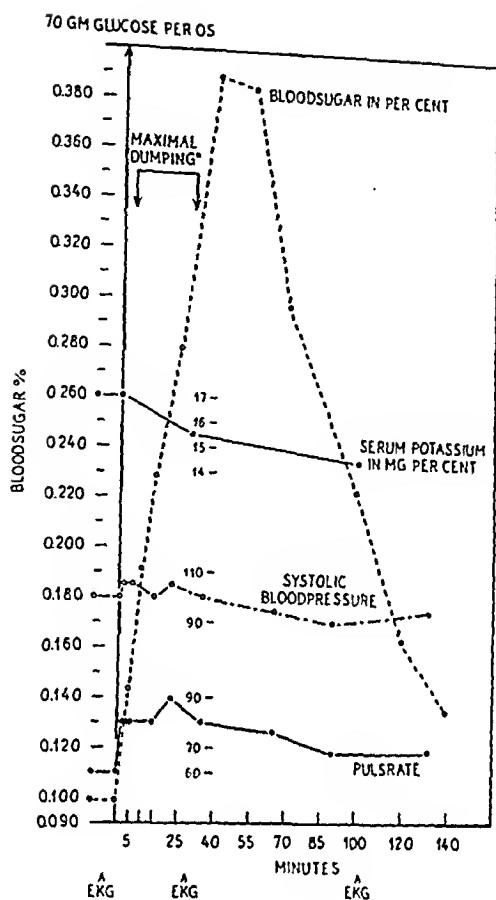


Figure 5. Case 5: Blood sugar (after 70 gm of glucose given by the mouth), serum potassium, systolic blood pressure, pulse rate, and electrocardiograms taken before and during the experiment.

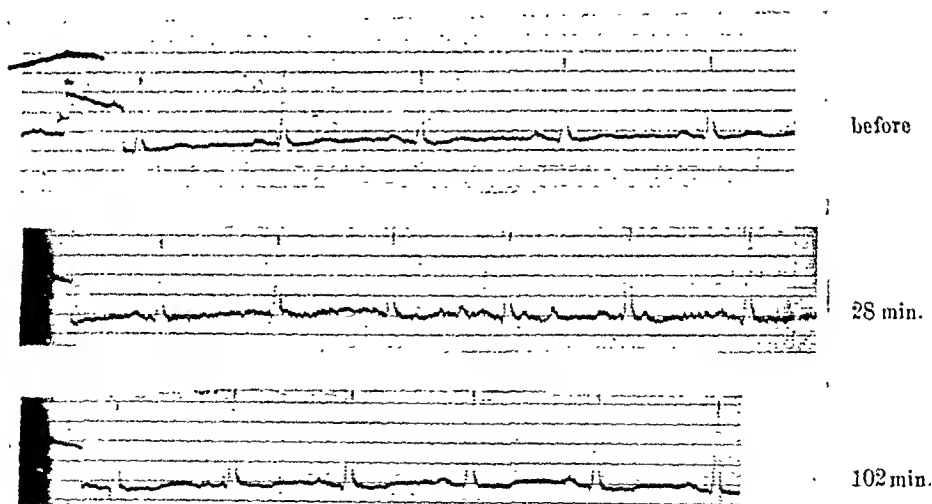
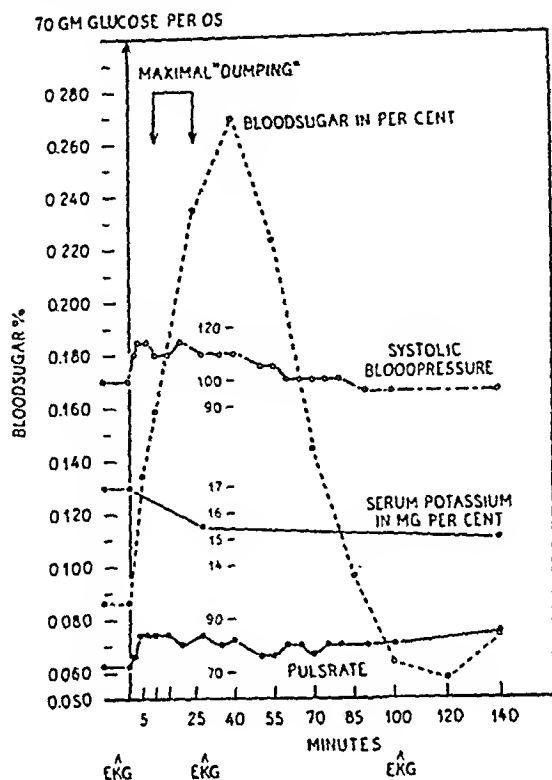


Figure 6. Case 6: Blood sugar (after 70 gm of glucose given by the mouth), serum potassium, systolic blood pressure, pulse rate, and electrocardiograms taken before and during the experiment.

The arrows in Figure 6 indicate the time of maximal malaise. The fall in the serum potassium does not explain the symptoms. An electrocardiogram recorded after 28 minutes shows accelerated action, negative T waves and slightly depressed

S—T intervals. The Q—T curve was unchanged. After 102 minutes (during the hypoglycaemic phase) the T waves and the S—T intervals had become iso-electric. U waves were present. The blood sugar curve reached its maximum at 0.270 per cent. in 40 minutes. There was a pronounced hypoglycaemic phase. Pulse rate and blood pressure reached a maximum in 5—20 minutes.

(B) *Intravenous glucose tolerance test.*

None of the patients felt any discomfort. All blood sugar curves were normal. No variations were observed in pulse rate, blood pressure, serum potassium or in the electrocardiogram.

Discussion.

In the peroral glucose tolerance tests, there was no alteration in the concentration of serum potassium in relation to the attacks; all potassium curves at the time of maximal malaise were within the normal range. The attacks therefore cannot be attributed to abnormal serum potassium values. The glucose curves are characteristic of patients who have been subjected to gastrectomy (Evensen (3)).

However, in the course of the attacks there appeared electrocardiographic changes similar to those found by Smith (13); these were of the following nature:

(1) An increase of the frequency, (2) flattening of the T waves, and (3) depression of the S—T intervals. It was pointed out by Smith (13) that he had been unable to demonstrate prolonged Q—T intervals; this was also confirmed by the present investigations. Smith (13) considers these changes to be indicative of hypopotassaemia, which is decidedly at variance with the potassium curves reproduced here.

What is then the underlying cause of the electrocardiographic changes? According to Sjöstrand (11, 12) an increased content of adrenaline in the blood may lead both to flattening of the T waves and depression of the S—T intervals. He stresses the difficulty in distinguishing electrocardiographically between an increased adrenaline concentration in the blood (or, perhaps better, an increased sympathetic tonus) and a hypopotassaemia; as the most essential difference he mentions that in the latter condition the Q—T intervals are prolonged, whereas they remain uninfluenced by a high adrenaline concentration.

Considering this, and comparing the findings with the clinical picture (the rise in the blood pressure, the tachycardia and the vasomotor symptoms), it seems reasonable to attribute the electrocardiographic changes to an increased sympathetic tonus.

The intravenous glucose tolerance tests all indicate that the intermediary carbohydrate metabolism is normal.

Attempts to provoke attacks with treble isotonic solutions of sodium chloride (two patients), galactose (two patients) and magnesium sulphate (four patients) as well as with distilled water (four patients) gave the following results:

The administration of sodium chloride and galactose gave rise to slight dumping attacks with a slight rise in the pulse rate and the systolic blood pressure. The symptoms were much fewer and of shorter duration in these attacks than in those

produced with glucose in the same patients. The administration of magnesium sulphate and distilled water did not give rise to dumping in any case. Considering this, the writer is inclined to attribute a specific pathogenetic importance to glucose.

Roentgenological examination of the stomach in these patients whose condition was similar to a very high degree showed normal emptying in the three and rapid emptying in the other three. It is impossible on the basis of the present series to arrive at a knowledge of the value of the roentgenological examination in estimating the rate of emptying. But the findings seem to support a supposition which has been previously put forward in a discussion in *The Lancet* (14); according to this, the rather viscous contrast medium will hardly be dealt with in the stomach stump in the same manner as the more liquid articles of food, so that the roentgenological examination does not to the full afford the information desired.

It seems equally difficult to explain important points in the pathogenesis of the syndrome. The very frequent complaint of oppression and fulness in the epigastrium, can undoubtedly be explained by a distension of the portion of the jejunum immediately next to the anastomosis (cf. the experiences of Butler and Capper (2) and Goligher and Riley (5) in distension of the jejunum with a balloon, by means of which they were able to produce this fulness but very seldom the other symptoms). The rise in the blood pressure, the tachycardia, the vasomotor symptoms and the electrocardiographic changes apparently suggest an increased sympathetic tonus. But how can the fatigue and the sleepiness be explained? Presumably also by the increased sympathetic tonus. The writer considers that this view is justifiable, as there is a very great resemblance, between the early stage of shock, when the sympathetic tonus only is increased, and a pronounced attack of dumping.

The essential problem is then: How does the increased sympathetic tonus arise?

Apparently a distension of the jejunum is not the only explanation.

On the basis of the present investigations it is tempting to postulate the presence in the jejunal wall or the portal area of gluco- or osmoreceptors which in the presence and resorption of articles of food, especially those with a high proportion of glucose, give rise to the liberation of a humoral factor.

Summary and Conclusions.

Roentgenological examination of the stomach, peroral and intravenous glucose tolerance tests were made in 6 patients with pronounced dumping symptoms. In some of the patients, provocation experiments were made with hypertonic magnesium sulphate, sodium chloride and galactose solutions, and with distilled water.

In the course of the glucose tolerance tests the blood sugar, pulse rate, systolic blood pressure, serum potassium and electrocardiogram were followed; otherwise only the pulse rate and the systolic blood pressure were recorded.

The results of these experiments led to the following conclusions:

- (1) Hypopotassemia can be excluded as a pathogenetic factor; see Figures 1—6.

(2) The electrocardiographic changes (a rise in the frequency, flattening of the T waves and depression of the S—T intervals) are due to increased sympathetic tonus.

(3) The intermediary carbohydrate metabolism is normal in patients with dumping.

(4) Glucose apparently exerts a specific effect as a provocative factor.

(5) Presumably roentgenological examination does not afford adequate information about the rate of emptying of the stomach stump.

(6) With regard to the pathogenesis of the syndrome, it can only be concluded that during the attacks there is to all appearance a hyperactivity of the sympathetic nervous system. The question as to whether the condition is the result of a mechanical or a chemical influence cannot be settled. There is presumably an interaction between mechanical and chemical forces.

References.

1. Alvarez, W.: *Gastroenterology* 13, 212, 1949. — 2. Butler, T. J. and Capper, W. M.: *B. M. J.* 1, 1177, 1951. — 3. Evensen, O. K.: *Alimentary Hypoglycaemia after Stomach Operations and Influence of Gastric Emptying on Glucose Tolerance Curve*. Oslo 1942. — 4. Faber, M.: *Ugeskr. Læger* 114, 12, 1952. — 5. Goligher, J. C. and Riley, T. R.: *Lancet* 262, 630, 1952. — 6. Jorgensen, Stefan: *Intravenöse belastninger med sukkerarter*. København 1930. — 7. Macbella, T. E.: *Ann. Surg.* 130, 145, 1949. — 8. Munck, O.: *Nord. Med.* 48, 1031, 1952. — 9. Pulvertaft, C. N.: *Lancet* 262, 225, 1952. — 10. Schechter, S. E. and Neeheles, H.: *Gastroenterology* 12, 258, 1949. — 11. Sjöstrand, T.: *Nord. Med.* 46, 1836, 1951. — 12. Sjöstrand, T.: *Acta Physiol. Scand.* 24, 247, 1952. — 13. Smith, W. Hamilton: *Lancet* 261, 745, 1951. — 14. Discussion. *Lancet* 260, 776, 1951.
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Evaluation of Corticotrophine (ACTH) in Patients.

By

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(Submitted for publication, October 1, 1953.)

Introduction.

The application of corticotrophine (ACTH) has presented a new kind of therapeutical problem, for we do not apply a drug directly, but by the administration of corticotrophine the body is stimulated to produce the active agent. Besides the normal variations in effective dose, which we know from other drugs and which are dependent on variable intake, excretion, breakdown and detoxification of the drug and sensitivity of the diseased tissue, in this case we are dealing also with other variables. We do not know what quantity of the therapeutic product is actually applied because we do not know how the adrenals react to the administration of corticotrophine and what individual variations there are in the secretions of the adrenal products under the influence of corticotrophine.

Corticotrophine is standardised according to the Sayers test (the vitamin C depletion of the adrenal in hypophysectomised rats). It is questionable if one is justified in assuming that this is a good criterion of the glucocorticoid production by the adrenals after application of corticotrophine in men. In other words the problem arises as to whether different batches of corticotrophine of similar strength, expressed in Sayers Units, are also of a comparable cortical-stimulating potency. There is no reason to assume a priori that the ascorbic acid depletion of the adrenal is a standard of the glucocorticoid producing-effect. We will not discuss here the general problem of comparability of effects in test animals and those in men. Should one wish to study the action of corticotrophine in different patients suffering from chronic disorders the results can only be comparable if an equal glucocorticoid production is obtained because this is actually the active agent.

There is an extreme divergence in the required effective clinical doses reported

This work was done with the aid of grants from the National Health Council.

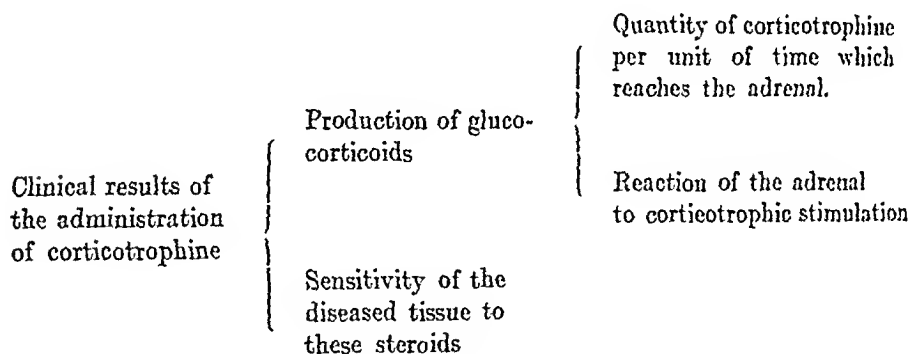
We are much indebted to Messrs. Organon for the use of data about some laboratory tests.

¹ Research fellow in medicine, National Health Council.

in the literature. In our clinical experiments we observed that several patients, receiving a given batch reacted less effectively than expected to a given dose I. U. (= Sayers Units). We therefore investigated the activity of different batches. Since then some articles in the literature have dealt with this problem (Ansell and Bywaters, 1952, Kaine 1952, Ogryzlo et al. 1953). The first two of these authors compared equal quantities of different batches with their clinical effect in patients with rheumatoid arthritis. Kaine used as a criterion in comparison with the Sayers test the drop of eosinophils and the 17-ketosteroid production in normal people. Ogryzlo investigated the decrease of eosinophils and the 17-ketosteroid production in patients with rheumatoid arthritis. All authors found a discrepancy between the indicated Sayers test units and the activity found in patients or normal people.

I. Criteria that can be used as a measure of the stimulation of the adrenal to secretion of glucocorticoids.

The factors upon which the clinical results of the administration of corticotrophine depend are presented in the following diagram.



In the evaluation of corticotrophine stimulation we will take certain possible criteria under consideration.

a. Clinical effect as a criterion.

The correct evaluation of the clinical effect is always extremely difficult in chronic diseases as for instance in rheumatoid arthritis, whose spontaneous course can be very variable and in which subjective factors can strongly influence the clinical picture. No exact quantitative comparison can be based on the subjective feeling of recovery.

Besides observing the subjectively reported improvement which usually appears even soon after a short administration of some days one can attempt to obtain objective measures of improvement by the use of function tests. Whenever these objective data are based on performance one should not forget that these are very strongly influenced by the presence or absence of the subjective sensation of pain. Therefore one obtains for the greater part an objective registration of subjective

feeling of pain and that in an inverse relationship. Really objective measures of decreased activity of the pathological process are: decrease of joint swelling, decrease of the sedimentation rate of the erythrocytes, increase of the haemoglobin level etc. These measures give as a rule too small differences in brief periods of administration.

In a biological assay, in which objective clinical improvement is used as a criterion, the testing of different batches on the same patient will take a long time. The great objection then arises that a change in clinical reactions could be ascribed to the spontaneous course of the disease. This makes comparisons extremely difficult. However the greatest and most essential objection to this criterion is that the clinical results are not only dependent on the glucocorticoid production of the adrenal but also to the sensitivity of the diseased tissue of different patients to these steroids (see diagram). With insensitive tissue a large steroid production gives little or no clinical effect whereas with very sensitive tissue even a slight production can give a very good clinical effect.

Relevant to this possibility is Kersley's observation (1952). He describes a patient suffering from rheumatoid arthritis which disease in spite of a decreased eosinophil count in the blood, elevation of the 17-ketosteroid excretion in urine and a use of the quantity of circulating 17-hydroxycorticosteroids in plasma still did not react to corticotrophine.

We believe this criterion for a biological assay of corticotrophine to be useless. This does not preclude the use of objective clinical improvement in the treatment of a given case.

b. 17-hydroxycorticoids in the peripheral blood as a criterion.

The estimation of these products although technically very difficult is possible according to the method described by Nelson et al. (1951). Besides the fact that large blood samples must be taken for this estimation (ca 30 ml) there are for the purpose desired a number of other objections to this method.

The level of the 17-hydroxycorticoids is determined among others by the following processes:

- a. the production of these compounds by the adrenal cortex.
- b. the consumption rate of the peripheral tissue.
- c. the degree of breakdown by the liver.
- d. the excretion rate by the kidney.

When we desire to draw any conclusions about production by the estimation of the blood level of the 17-hydroxycorticoids then it is necessary to know for certain that the rates of the last three processes are of no value or be able to demonstrate their very slight individual variations. As regards these there are no known data but it appears that the clearance rate of cortisone and hydrocortisone from the circulation is very high (Nelson et al. 1952). Therefore in our opinion the use of the above mentioned criteria for comparison of corticotrophine activity is not feasible.

One can attempt to obtain an indication of the corticoid production of the adrenals by indirect means.

1. Eosinophil count in the peripheral blood as a criterion.

One effect of increased corticoid secretion is the decrease of eosinophils in the peripheral blood. Conversely one can attempt to measure the amount of adrenal activity by this decrease. It appears that there are many disadvantages involved in this method, which make it impossible to obtain mutually quantitatively comparable measures of the adrenal activity. First there is a strong variability of the

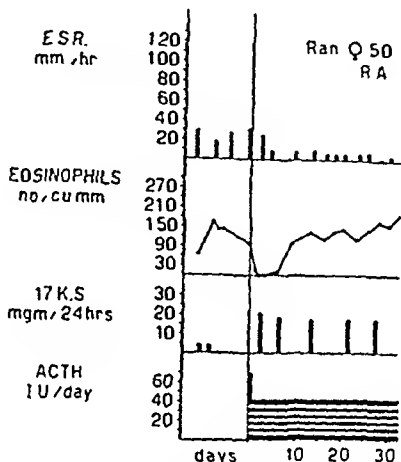


Fig. 1. Absence of correlation between the eosinophils in the blood and the 17-ketosteroid excretion in constant ACTH therapy.

base line of the eosinophils; the level of eosinophils in the blood shows great oscillations, not only from patient to patient but also from hour to hour in the same patient a. o. (Bonner 1952).⁴ The eosinophils can completely disappear with small doses corticotrophine only.⁵ Even were it possible to predict these spontaneous variations we still see from figure 1 that the eosinophil leucocytes are useless in evaluation of the activity of the adrenal.

With corticotrophine a good clinical remission was obtained in a 50-year-old woman suffering from rheumatoid arthritis. This was accompanied by decrease of the sedimentation rate. The sedimentation rate, next to the eosinophil leucocytes and the 17-ketosteroids is presented in the graph as a measure of the reaction of the patient to a constant dosage of corticotrophine per day. With the same dosage the eosinophils returned to pre-treatment levels in the second week of treatment. The clinical condition and the unaltered high secretion of the 17-ketosteroids per 24 hours were maintained. It therefore appears that the corticotrophine effect was definitely present in spite of the fact that the eosinophils rose again to their previous level.

2. The excretion of corticoids in urine as a criterion.

This estimation seems attractive in theory. However against the methods which are at present available (Heard et al. 1946, Daughaday et al. 1948), many objec-

tions have been raised. Even in Cushing's disease, in which an increased glucocorticoid production must be assumed, frequently normal corticoid values in urine are found.

As result of many investigations in this field (Marrian, 1951) the hope appears to be justified that a great deal of these objects in the future can be overcome. A revaluation of this method of estimation shall then be necessary.

3. The neutral 17-ketosteroids excretion per 24 hours as a criterion.

This estimation is also an indirect measure of the adrenal activity. It should however be realised that the 17-ketosteroids are also metabolic products of the androgens. In spite of this they may be considered to be the best method for evaluation of adrenal activity for the following reasons.

Table 1.

Effect on the 24 hour excretion of 17-ketosteroids after i. m. administration of 6×7 I. U. corticotrophine of the same batch, during two periods of three days in the same patient.

Pt.	Batch	17-k. s. mg/		Period in between	17-k. s. mg/	
		control day	3rd day		control day	3rd day
1. v. K.	22/G	3.5	¹ 19.2	11 days	4.0	23.8
2. Ste.	Res. P 146	6.4	11.0	15 days	3.7	12.1
3. M.	27/1/3	8.0	11.3	14 days	5.9	13.7
4. Ra.	22/G	13.8	55.9	25 days	13.9	27.5
5. P.	22/G	7.9	34.1	50 days	9.0	34.2
6. P.	37A	9.7	28	12 days	8.6	23.8
7. Ste.	41A	6.4	14.3	10 days	10.0	16.1
8. v. H.	16/4/F	7.9	25	15 days	10.0	16.7
9. V.	41A	16.0	23.1	15 days	13.2	25.1

¹ 2nd day.

The estimation is technically quite feasible and reproducible. If the real total 24-hours output is collected it appears that patient for patient constant values are obtainable, in other words there is an individual constant baseline. From table 1 it may be concluded that a given corticotrophine batch injected in the same dose at varying intervals in the same patient will give values of response which considering the biological variations are quite acceptable, thus the ability to reproduce the same result using the same dose of corticotrophine is satisfactory. The reaction seems to be sensitive. After a dose of 6×7 I. U. corticotrophine per day an increase of up to 620 % of the baseline can be seen and even with low dosages of 6×2 I. U. per day a rise of up to 230 % is observed (see table 2).

Does the 17-ketosteroid excretion have any correlation with the glucocorticoid production? A direct proof is impossible, because quantitative estimation of the latter is not yet available (vide supra). There are however some indirect indications. It appears from figure 2 that over a short period of administration (3 days) there is a simultaneous increase of 17-ketosteroid production with decrease in the eosinophils. The variations of the 17-ketosteroids are the more sensitive of the two and show a greater range of fluctuation in values.

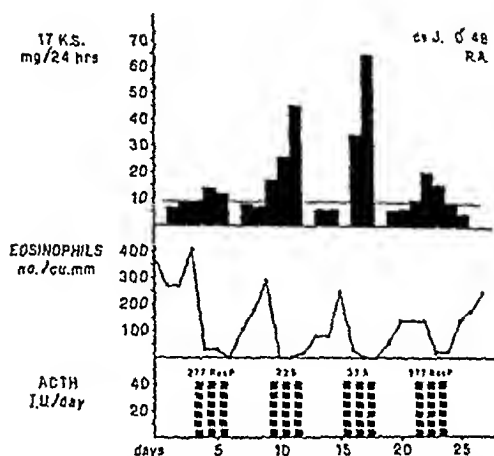


Fig. 2. Administration of the same amount of corticotrophine of different batches in the same patient with nearly 100 % decrease of the eosinophils and at the same time a difference in the increase of the 17-ketosteroids in the 24 hour production.

In fig. III is shown that after 3 days of intramuscular and intravenous infusion there is a disappearance from the blood of eosinophils in each case but there is a difference in degree of stimulation of the 17-ketosteroid excretion. The same is seen in fig. IV during three days of intravenous infusion or injections. Three days

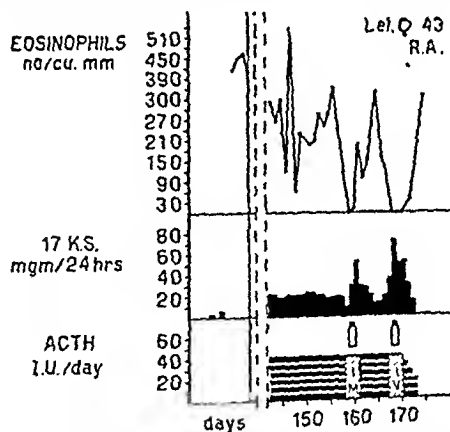


Fig. 3. Showing the effect of 42 I. U. of corticotrophine administered during 3 days as an intramuscular and intravenous infusion in a patient with rheumatoid arthritis who had become resistant to 6×7 I. U. corticotrophine/day intramuscularly.

of intramuscular infusion gives a small increase of the 17-ketosteroids and no decrease of eosinophils. In our patients the clinical condition correlated well with the change in the 17-ketosteroid excretion. We observed several times that during prolonged administration of a certain batch, which was clinically less effective than expected, there was a reflection of the poor response in the 17-ketosteroid excretion. For this reason we believe that at the present moment the 17-keto-

steroid excretion should be accepted as a satisfactory criterion for adrenal activity in men under corticotrophine stimulation.

II. *Conditions under which the use of the 17-ketosteroid excretion can serve as a criterion.*

It must be first realised that there is great individual variation in the increase of the excretion of the 17-ketosteroids in the urine after an injection of the same amount of corticotrophine of the *same batch* (illustrated in table 2). This strongly variable adrenal reaction in different patients makes it obligatory that *different batches* of corticotrophine be administered to the *same patient* in order to be compared. The glucocorticoid production (for which we have accepted the 17-ketosteroid excretion as an indirect measure) is dependent on two factors. These are the quantity of corticotrophine which reaches the adrenal per unit of time and secondly the reaction of the adrenal to corticotrophine (see diagram). Both factors can themselves be influenced by various others. Concerning the problem of corticotrophine «resistance» some of these possible factors were studied by us (Goslings 1951 (a) and (b)) and discussed in a previous publication (Goslings 1952).

We will here consider only some of the factors which influence the quantity of corticotrophine reaching the adrenal per unit of time *i. e.* the quantity of corticotrophine which is administered per unit of time and the methods of administration. It is well known that corticotrophine disappears rapidly out of the blood (Sayers et al. 1949, Greenspan et al. 1950, Sonenberg et al. 1951). Experience has taught us that a rapid stimulation of the adrenal activates it only for a short time. It is therefore of importance to know how much corticotrophine reaches the adrenal per unit of time.

Either fractionated administration or infusion of a given quantity of corticotrophine will thus have a stronger adrenal stimulating effect than a single injection. The theoretical consideration (de Jongh et al. 1950) is experimentally established (McIntosh et al. 1951, Querido et al. 1951, v. Creveld et al. 1950, Hamburger et al. 1951).

The general conclusion which may be drawn from these experiments is that corticotrophine works far more effectively when the administration is divided over a large number of injections or when given by intravenous infusion. Although these general considerations can be simply stated, detailed analysis will confront us with new problems. According to Gordon et al. (1951) the route of administration may be decisive. This was a surprise to us because in both cases previously studied by us (Querido et al. 1951) no marked difference was observed between frequent intramuscular injections and intravenous infusion with regard to the 17-ketosteroid response. One objection to this argument is that in each patient a maximal stimulation of the adrenal was reached with the doses of corticotrophine used so that no further differentiation was possible.

The observations of Gordon were sufficient reason for us to reinvestigate the influences of the route of administration. In patients (fig. 3 and 4), who no longer responded adequately to a daily dosage of 6×7 U. intramuscularly («resistance»), a similar daily dose was administered as a constant intramuscular and

intravenous infusion during three days and in one patient also in 6 daily intravenous injections. It appears from the graphs that intravenous infusion produces the strongest effect, followed in order by fractionated intravenous injections, intramuscular infusions and finally fractionated intramuscular injections.

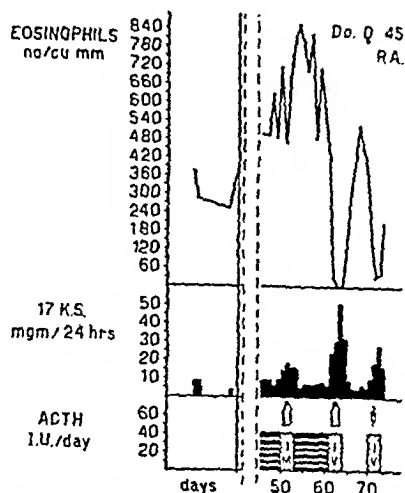


Fig. 4. To show the effect of 42 I. U. corticotrophine administered during 3 days as an intramuscular and intravenous infusion (and divided into 6 intravenous injections) in a patient with rheumatoid arthritis who had become resistant to 6×7 I. U. corticotrophine/day intramuscularly.

The investigations of Adams et al. (1951) suggest that protease impurities in the preparations may be activated during incubation in muscle. Pincus et al. (1952) discuss a neutralizing factor in the serum. However this cannot be the only or decisive factor. It is difficult to envisage a muscle factor which during intramuscular infusion does not operate and a serum factor which has less effect on intravenous than intramuscularly administered corticotrophine.

By the use of purer, more recently developed preparations (Rosenberg et al. 1951), the differences between intramuscularly and intravenously administered corticotrophine were less pronounced (Council on Pharmacy and Chemistry 1953). According to investigations by Organon Inc., the corticotrophine preparations used by us never contained protease. In our opinion the above mentioned order of effectiveness of different methods of administration can for the greater part be explained adequately by the different quantities of corticotrophine reaching the adrenal.

In our opinion the arguments advanced are insufficient to constitute a more essential difference between various methods of administration. Thus one can employ different methods of administration for this biological test providing that the same test procedure and same method of administration are always used.

Methods.

A test method in which the different batches examined during three consecutive days were administered intramuscularly in 6 fractionated doses of 7 I. U. per day

was developed. These periods were alternated with control periods of three to five days in which placebo injections were administered. The total 24 hours urine production was collected daily and examined for 17-ketosteroid excretion. Creatinine excretion was determined in a number of patients in order to control urine collection. The daily dose should be chosen such that no maximal response is obtained. The more or less arbitrarily selected quantity of 6×7 I. U. was generally adequate.

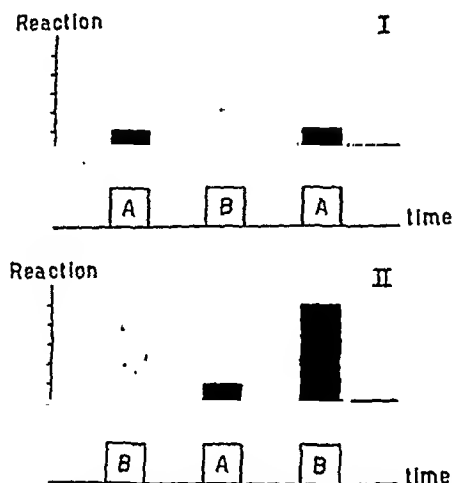


Fig. 5. Scheme by which different batches are compared.

This dose was clinically effective in most patients in spite of the fact that the dose was much smaller than that advocated in many publications. With the intramuscular dose of 6×2 I. U., though often clinically effective the 17 k. s.

Table 2.

The variation in the excretion of 17-ketosteroids in different patients after administration of 6×7 I. U. compared with 6×2 I. U. corticotrophine/day of the same batch during three days.

6 × 7 ch. 22/G				6 × 2 ch. 22/G			
Pt.	Before (mg/24 h.)	After (mg/24 h.)	Increase %	Pt.	Before (mg/24 h.)	After (mg/24 h.)	Increase %
Sc.	10.2	20.0	100	Bo.	3.6	2.8	- 20
St.	10.0	21.1	110	Gee.	4.0	4.0	0
Gu.	7.0	18.5	120	Kor.	7.6	13.0	70
C.	8.7	24.0	180	Ko.	7.2	12.9	80
Ge.	8.0	24.1	200	Koo.	7.9	16.1	100
Kin.	4.2	12.7	200	v. Ka.	4.3	13.7	220
V.	11.8	35.3	200	Mu.	16.0	53.3	230
Ra.	13.8	55.9	310				
P.	7.9	34.1	330				
r. R.	6.0	31.8	430				
Mi.	4.7	26.5	450				
L.	4.8	28.2	500				
Sw.	4.2	30.5	620				

response may be small. A dosage of 6×4 I. U. may even be more suitable than our dosage of 6×7 I. U.

In conclusion it must be realised that after several series of injections the 17-ketosteroid response may become less. It is therefore necessary to end with the first employed preparation if different corticotrophine preparations are compared. We employ the following scheme (indicated in fig. 5). With similarly occurring 17-ketosteroid reactions of A and A or B and B one may compare the interposed preparations.

III. Comparison of different batches of ACTH.

Is there any reason to presume a lack of parallelism between activity expressed in Sayers Units and the activity observed in the clinical test?

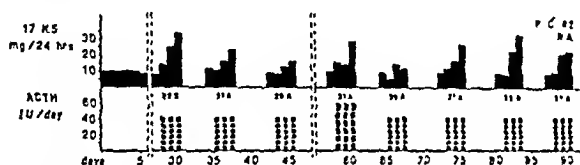


Fig. 6. Comparison of different batches of corticotrophine injected in the same patient at different times. For doses see discussion.

To study this problem we used the technique as indicated and discussed under II (three day injection-periods alternating with 3—5 day placebo-periods).

In fig. 6 the behaviour is shown of different batches injected at a level of 6×7 I. U. daily. The 17-ketosteroid excretion during the period that the batches 22 and 37 were applied was of the same magnitude. These batches produced con-

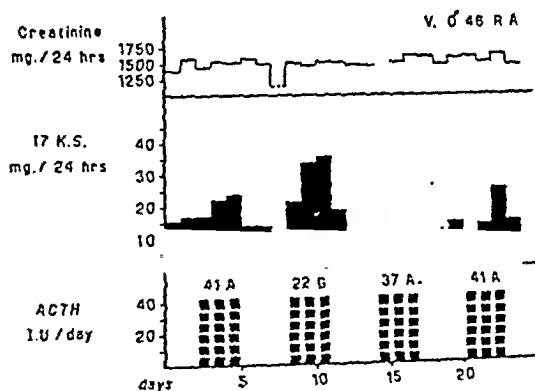


Fig. 7. Comparison of different batches of corticotrophine injected in the same patient at different times. For doses see discussion.

siderably more increase of 17-ketosteroid excretion during this 3 day period than equal doses of batches no. 29, 31 and 36. The 17-ketosteroid excretion resulting from preparations 22 and 37 was approached when we used 6×10 I. U. instead

of 6×7 I. U. of batch 31. The similarity of response in batches 22 and 37 is also apparent in fig. 7. Batch 41 had definitely less effect on the 17-ketosteroid excretion than batches 22 and 37.

Discrepancy between the various batches which manifested itself in this biological assay by the 17-ketosteroid excretion runs roughly parallel to the clinical effect, even though this is much more difficult to report in figures. This parallelism is supported by the following observation. Two patients were simultaneously and similarly treated with increasing doses of 6×2 , 6×3 , 6×4 I. U. corticotrophine of batch 27. During treatment with batch 27 there was in both patients neither an increase in the 17-ketosteroid excretion nor a drop in the eosinophil count neither was there improvement in the clinical condition. Because of the poor clinical effect a new batch (22) was employed after 91 days, also in doses of 6×4

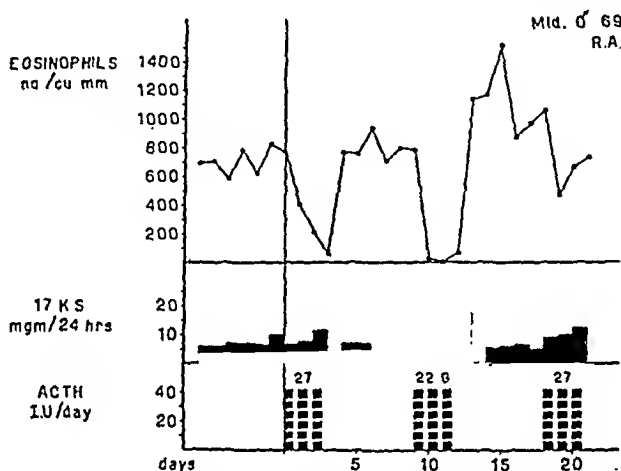


Fig. 8. Comparison of different batches of corticotrophine injected in the same patient at different times. For doses see discussion.

I. U. After treatment with batch 22 both patients showed a definite 17-ketosteroid response accompanied by improvement of the clinical condition and a decrease of the sedimentation rate.

Stimulated by this clinical finding we subjected these batches to the 3 day test. Fig. 8 shows that batch 22 in the same dosage has a much stronger effect on the 17-ketosteroid excretion than batch 27.

Similar observations of inferior clinical effect were made with 6 patients treated with batch 31. The inferior behaviour of this batch in the 17-ketosteroid test is demonstrated in fig. 6. As a last example we refer to fig. 2. In this experiment the 17-ketosteroid response during the period of administration of batches 22 and 37 was noticeably higher than during administration of batch Res. P 277.

In table 3 the amount of 17-ketosteroids excreted during the 3 day periods of administration of the different batches is given in mg exceeding the value of 3 days of the mean control. Although we know that it is not permitted to attach too much value to this way of expressing results it serves the purpose of giving an impression of the increase. We consider ourselves justified in concluding that

different effects in 17-ketosteroid excretion can be observed in different preparations injected in identical quantities under identical conditions.

Table 3.

Total mg increase of 17-K. S. in mg exceeding average control values during the three days of injection.

de J.				
batch	$\frac{277}{14.2}$	$\frac{22}{67.8}$	$\frac{37}{81.6}$	$\frac{277}{25.7}$
17-K. S.				
Mid.				
batch	$\frac{27}{3.9}$	$\frac{22}{33.1}$	$\frac{27}{8.1}$	
17-K. S.				
V.				
batch	$\frac{41}{21.3}$	$\frac{22}{48.9}$	$\frac{37}{60}$	$\frac{41}{9.2}$
17-K. S.				
P.				
batch	$\frac{22}{46.2}$	$\frac{31}{13.8}$	$\frac{29}{10.6}$	$\frac{31}{31}$
17-K. S.				
batch	$\frac{36}{4.3}$	$\frac{37}{29.6}$	$\frac{22}{38.5}$	$\frac{37}{28.2}$
17-K. S.				

¹ only second and third day.

Discussion.

The discrepancy observed in some batches between the activity expressed in Sayers Units and the activity in the clinical test may be explained in different ways.

1) Obviously there are at least two demonstrable causes for possible quantitative differences. Firstly the results in the Sayers test are subject to very large deviations. Because of this variability deviations of 50 % from the actual strength of the preparation can occur in exceptional cases.

Secondly in the absence of the same constant international standard preparation, assaying of corticotrophine has often been done against different standard preparations a practice which in itself can also lead to deviations. Some preparations which deviated in the clinic (batches 27, 29, 31) were for this reason kindly re-assayed by Messrs. Organon against new standard preparations. It then appeared that a large part of the observed discrepancies could indeed be explained. The results of the re-assay correlated more closely with the clinico-biologically determined strength. We did not in fact give 42 I. U. using these batches but much less. This result strengthens the case for the quantitative value of this clinical test on the 17-ketosteroid excretion, which test brought the wrong labelling to light.

2) Moreover the possibility exists that the discrepancies observed are an indication of qualitative differences between the Sayers test and the clinical test mentioned above. This might *c. g.* depend on the fact that in the Sayers test the corticotrophic effects are evaluated by other means than by the clinico-biological

test. There is little known about the connection between ascorbic acid decrease in the adrenals and steroid production after ACTH stimulation.

However the influence of the factors mentioned under 1) is great and the results of the clinical test are also subject to variation. Without further results and discussions there is therefore no reason to conclude yet that the qualitative deviations mentioned under 2) were also operating factors.

We feel that the data obtained with batch Res. P 277 could be an indication that qualitative differences also exist. This batch was prepared by a special procedure differing entirely from the usual procedure used for commercial preparations. The preparation was exclusively intended and used for experimental purposes. The preparation showed a discrepancy between both tests. The batch Res. P 277 was also assayed in the adrenal weight maintenance test by Messrs. Organon. It is interesting to note that this test showed for this preparation better correlation with the clinical 17-ketosteroid excretion test.

For comparative clinical scientific research the use of *one single batch* is obligatory. If this is not possible before using a new batch one should test the effectiveness of this batch against the former, in the clinical biological test.

Summary.

When administering corticotrophine we have besides the normal pharmacological variability also to do with an other unknown factor.

In the administration of this drug we do not give a direct therapy but stimulate the body to produce the active agent.

The criteria which may indicate the activity of the administered corticotrophine, are discussed.

From this paper it may be concluded that nowadays the best measurements available are the 24 hours excretion of the 17-ketosteroids. From the results of our clinical investigations the suspicion arose that not all the corticotrophine preparations were of the same strength. By means of the 24 hours excretion of the 17-ketosteroids as criterion different batches of corticotrophine were tested.

According to this clinico-biological test the conclusion was drawn that some batches show a divergence between the adrenal activation capacity and their label.

It is probable that next to quantitative failures inherent in the Sayers assay there are also qualitative differences in the evaluation of corticotrophine in different tests.

For comparative clinical scientific research the use of *one single batch* is obligatory. If this is not possible one should before using a new batch test the effectiveness of this batch against the former in the clinico-biological test.

Literature.

Adams, E. and Smith, E. L.: *J. Biol. Chem.* **191**, 651, 1951. — Ansell, B. M. and Bywaters, E. G. R.: *Ann. Rh. Dis.* **11**, 213, 1952. — Bonner, C. D.: *J. A. M. A.* **148**, 634, 1952. — Council on Pharmacy and Chemistry. *J. A. M. A.* **151**, 474, 1953. — Creveld, S. v. and Kuipers, F.: *N. T. v. G.* **94**, 2175, 1950. — Daughaday, W. H., Jaffe, H. and

Williams, R. H.: *J. Clin. Endocrinol.* 8, 166, 1948. — Gordon, E. S., Kelsey, C. and Meyer, E. S.: *Proceedings of the Second Clinical ACTH Conference*. The Blakiston Company, New York 1951, Vol. II, p. 30. — Goslings, J., Hijmans, W., Querido, A. and Kassenaar, A. A. H.: II Congresso Europeo de Reumatologia, Barcelona, 1951 *Comunicaciones Editorial Scientia* 162—171. — Goslings, J., Hijmans, W., Querido, A. and Kassenaar, A. A. H.: *Brit. Med. J.* II, 698, 1951. — Goslings, J., Querido, A., Hijmans, W. and Kassenaar, A. A. H.: *Cortisone and ACTH, Symposium v. d. Ned. Ver. v. Endocrinologie, Seheltema en Holkema, N. N. A'dam* 1952, p. 84—92. — Greenspan, F. S., Li, C. M. and Evans, H. M.: *Endocrinology* 46, 261, 1950. — Hamburger, C., Sprechler, M., Broehner Mortensen, K. and Videbaek, A.: *Congresso Europeo de Reumatologia* 1951. *Ponencias oficiales* p. 177. — Heard, R. D. H., Sobell, H. and Venning, E. H.: *J. Biol. Chem.* 165, 1946. — Jongh, S. E. de, and Wijnans, M.: *Acta Physiol. Pharmacol. Neerl.* 1, 237, 1950. — Kaine, H. D.: *Proc. Soc. Exp. Biol. Med.* 81, 412, 1952. — Kersley, G. D., Mandel, L. and Desmarais, M. H. L.: *Brit. Med. J.* II, 540, 1952. — Marrian, G. F. and Cox, R. I.: *Biochem. J.* 48, XXXIII, 1951. — McIntosh, H. W. and Holmes, C. B.: *Canad. M. A. J.* 65, 33, 1951. — Nelson, D. M., Samuels, L. T., Williardson, D. G. and Tyler, F. H.: *J. Clin. Endocrinol.* 11, 1021, 1951. — Nelson, D. M. and Samuels, L. T.: *J. Clin. Endocrinol.* 12, 519, 1952. — Ogryzlo, M. A. and Gornall, A. G.: *J. Clin. Endocrinol. and Metab.* 13, 165, 1953. — Pincus, G., Hopkins, T. F. and Hechter, O.: *Arch. of Bioch. and Biophys.* 37, 408, 1952. — Querido, A., Kassenaar, A., Goslings, J. and Hijmans, W.: *Acta Endocrinol.* 6, 90, 1951. — Rosenberg, I. N., Cleroux, A. P., Raben, M. S., Payne, R. W. and Astwood, E. B.: *A. M. A. Arch. Int. Med.* 88, 211, 1951. — Sayers, G., Burns, T. W., Tyler, F. H., Jager, B. V., Schwartz, T. B., Smith, E. L., Samuels, L. T. and Davenport, H. W.: *J. Clin. Endocrinol.* 9, 595, 1949. — Souenberg, M., Keston, A. S. and Money, W. L.: *Endocrinology* 48, 148, 1951.

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Sensitivity Tests by Means of Diffusion Methods and their Clinical Interpretation.

By

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(Submitted for publication October 16, 1953.)

Introduction.

The choice of a suitable antibiotic is governed by two main questions:

1. Towards which of the available antibiotics do the bacteria, isolated from the patient, show a maximum sensitivity?

This may in a more exact form be expressed as: Which antibiotic has the lowest minimum inhibiting concentration (m. i. c.) for the bacteria isolated?

According to definition the m. i. c. is the highest dilution of antibiotic to cause bacteriostasis.

2. Is it possible to effect in the patient a serum level of the antibiotic at or above the m. i. c., needed for suppression of growth of the bacteria involved?

This paper attempts to express the results of sensitivity tests in terms of m. i. c. Further we have tried to gain information about the serum levels of the current antibiotics, by studying the pertinent literature, and by our own determinations using Heatley's plate method. The results permit an interpretation of sensitivity tests, which facilitates the choice of the suitable antibiotic in bacterial infections.

The Interpretation of Sensitivity Tests in Terms of Minimum Inhibiting Concentration.

From the different modifications, available for determination of bacterial sensitivity by means of a diffusion method, we chose the tablet method, devised by Lund (1, 2). This method is in our opinion very well suited for routine determinations, because of its technical simplicity and because of the relatively short reading time required.

According to the original description given by Lund, a homogeneous suspension

of the pure culture of the organisms, isolated from the patient, is made. This suspension is evenly spread on a 10 % Levinthal agar, by means of a glass rod. Then tablets, containing standardized amounts of the antibiotics to be tried, are placed on the inoculated agar and the plates are placed in the incubator at 37° C.

After 12 hours the diameter of the inhibition zone, formed around the tablet, is measured. Since this diameter will be proportional to the sensitivity of the bacteria to the antibiotics contained in the tablets, it will be possible to compare the action of different antibiotics on the bacteria to be attacked.

The interpretation of the inhibition zone, formed around the tablet, becomes difficult, when it is desired to find, whether a given, measured inhibition zone is large enough to justify a favourable prognosis for the treatment.

The Experimental Standardization by Dilution Test.

In the standardization of their sensitivity-tablets Lund and co-workers used an experimental method to arrive at a tentative interpretation of inhibition zones in terms of m. i. c. (2). In short their method amounts to comparing the results, obtained by their diffusion method, with the results found by determination of the m. i. c. by a dilution method.

The procedure is then as follows:

Supposing, that by a dilution method it is determined that the growth of the test bacteria *Staphylococcus P 209* is entirely suppressed by 0.2 I. U./ml penicillin, and that a tablet containing the standard amount of 50 I. U. penicillin, on a plate, inoculated with *Staph. P 209* yields an inhibition zone of 25 mm. It is then inferred, that an inhibition zone of 25 mm around a tablet, containing the standard amount of penicillin, means that the bacteria is susceptible to a m. i. c. of 0.2 I. U./ml.

Working with tablets, containing the following standard amounts:

Penicillin	50 I. U.
Sulphathiazole	2 mg
Streptomycin	5 "
Aureomycin	5 "
Chloramphenicol	5 "
Terramycin	5 "

Lund and co-workers arrived at the interpretation of inhibition zones, given in Table I.

This procedure is of course open to criticism, since the conditions involved in carrying out dilution tests, are in many respects different from the conditions found when employing diffusion tests.

In antibiotics with a mainly bacteriostatic action it is difficult to obtain a really sharply defined growth limit in the dilution test.

The size of the inoculum also, which is of rather less importance in diffusion methods, may influence the result of dilution tests to a considerable degree. (8.)

Table I.

Relation of inhibition zone to the minimum inhibiting concentration according to Lund, Funder-Schmidt a. o.

Diameter of Inhibition zone in mm	Minimum inh. conc. in γ /ml (or I. U./ml)			
	Sulpha	Penic.	Streptom.	Aureom. Terram. Chloramph.
16—24	100—50	5 —0.5	100—10	10—20
25—29	25—12.5	0.5—0.1	10— 2	20— 1
≥ 30	12.5	0.1	2	1

Though we feel, that by altering the experimental conditions in the dilution test (*e. g.* by reading the 50 % bacteriostatic concentration by means of a turbidimetric method, and by using a standard loop for inoculation of the test tubes) some of the difficulties named above may be overcome, we hoped to arrive at an adequate interpretation of inhibition zones on a more theoretical basis. We thought that it might be possible to apply the general theory of plate assays, given by Cooper, Humphrey, and Lightbown in their recent publications, to our problem (3, 4, 5).

The Concept of the 'Critical Time' Applied to the Interpretation of Inhibition Zones.

All diffusion theories try to calculate the concentration of the diffusing agent, present at different distances from the diffusion centre at a given time (t).

For the diffusion of antibiotics in agar media a formula has been derived by Liddiard. This formula has been based on the simplifying assumption, that, at the beginning of the experiment, a known quantity of antibiotic is being placed in the form of a very small pencil at the centre of diffusion. Moreover it is assumed, that radial diffusion takes place from this centre into the agar layer.

For a more detailed description of Liddiard's theoretical reasoning, we refer to the paper by Humphrey and Lightbown. It seems sufficient here to note, that the concentration of antibiotic, present at a certain time (t) at a distance (r) from the centre of diffusion, may be calculated, if we know:

1. the total amount of antibiotic placed into the agar,
2. the depth of the agar layer,
3. the diffusion-constant of water in agar at the temperature of the experiment.

With the aid of Liddiard's formula we are able to construct a graph in which every line represents the concentration of antibiotic (c) at distance (r) from the centre of diffusion, drawn for a certain chosen time after the beginning of the experiment (t). The line so constructed we call the r — c line, and in the following graph two such lines are shown as an example (graph I).

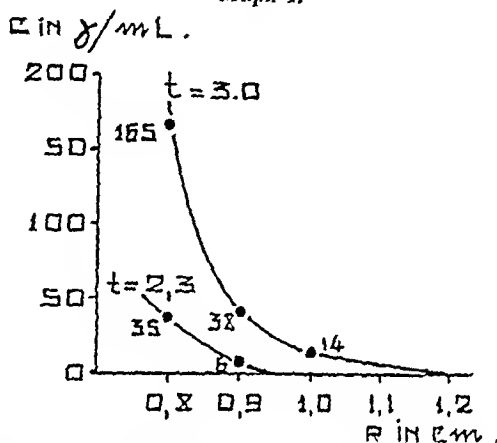
Before we are able to derive from our r — c lines an interpretation of inhibition

zones in terms of m. i. c. we must still consider two fundamental questions, which are already treated in the work of Cooper, Humphrey etc. (3, 4):

1. At which moment after the beginning of the experiment may we expect the inhibition zone to have reached its definite size?

2. If we know at which moment the inhibition zone is determined, is it then possible to find a correlation between the size of the inhibition zone as read, and the m. i. c. of the diffusing antibiotic for the bacteria under study?

Graph I.



Concentration of antibiotic in $\mu\text{g}/\text{mL}$ at 2.3 hrs and 3.0 hrs after the beginning of the experiment to be found at distance (r) from the diffusion centre. It is supposed here that 5 mg of antibiotic have been placed at the centre.

1) In experiments, done by Cooper and Gillespie (3) chiefly with strains of *Staphylococcus*, it appeared, that in the in-vitro experiments, after a certain «critical time», the bacteria are able to grow in the presence of many times the minimum inhibiting concentration. Bacteria which are reached by the m. i. c. before the critical time will be suppressed in their growth, while bacteria being reached by the m. i. c. after the critical time will show normal growth. It follows, that the size of the inhibition zone attains its definite value at the critical time discussed above; (in general this is at a time, when nothing can as yet be seen by the naked eye).

Since in Cooper's experiments the critical time appeared to be about 4 times the generation-time of the bacteria plus the lag phase (phase, preceding the phase of logarithmic growth), we arrive at the following values:

The generation-time of most bacteria found in routine specimens varies at 37°C between 20 min. and 40 min. The lag-phase of most bacteria falls within a time limit of about 60 min. So the critical times, with which we are concerned, are apt to vary between: $t = 4 \times 20 + 60 \text{ min.} = 2.3 \text{ hours}$ and $t = 4 \times 40 + 60 \text{ min.} = 3.7 \text{ hours}$.

2) From the reasoning explained above follows that we may expect the inhibition zone to occur at that distance from the diffusion centre, where at the critical time the m. i. c. is present.

It is now possible to find a relationship between inhibition zone and m. i. c. based on the r—c line (see above) and the concept of the critical time.

E. g.: Supposing the bacteria under study has a critical time of 3.0 hours. A tablet containing 5 mg of streptomycin causes an inhibition zone to occur of 20 mm diameter. Then at a distance of 10 mm from the diffusion centre the m. i. c. must have prevailed at the critical time (3.0 hours). Since the r—c line for the time of 3.0 hours shows the concentration of antibiotic at 10 mm distance from the centre to have been 14 γ /ml the m. i. c. of streptomycin for the bacteria is apparently 14 γ /ml.

We have constructed r—c lines for all generation-times between 20 and 40 minutes (representing critical times between $t = 2.3$ hours and $t = 3.7$ hours), using as the amount of antibiotic, present in the diffusion centre, the amount of antibiotic, contained in the tablets described above.

The construction of our diffusion graphs was done in the following manner:

Liddiard's formula is as follows:
$$\sigma = \frac{M}{4\pi hDt} e^{-\frac{r^2}{4Dt}}$$

In this expression the following terms are encountered:

σ = concentration of antibiotic at distance (r) from centre of diffusion (in mg/l or γ /ml).

M = amount of antibiotic placed at the centre of diffusion (in mg).

D = diffusion-constant of the antibiotic in the agar medium, which is approximately the same as the diffusion-constant of water in agar at the temperature of the experiment (in cm^2/hr).

t = time during which diffusion has taken place after start of the experiment (in hours).

h = depth of the agar layer.

In our calculation we applied the above as follows:

(M): As already stated, the formula has been derived on the assumption that the total amount of antibiotic placed at the diffusion centre is inserted into the agar as a pencil of infinitely small dimensions and that radial diffusion takes place. As (M) in our calculations we used the total amount of antibiotic present in the Lund-tablet. It is assumed that the antibiotic readily dissolves in the small water layer, always present on the agar surface and that diffusion of the antibiotic solution takes place in the manner described above.

(D): Since the diffusion-constant (D) does not seem to vary very much for different antibiotics, given a temperature of 37°C , and since small changes in the (D) term of the formula do not influence the outcome in a considerable way, a medium value of $0.01 \text{ cm}^2/\text{hr}$ seems appropriate here.

(h): As depth of the agar layer we used 0.4 cm.

(t): As time (t) we took the critical times, calculated on the assumption that for a certain bacteria with generation-time G. T. the critical time will be 4 times the G. T. plus the lag phase. Since at 37°C the lag phase is generally about 1 hour we arrive at our critical time (t) by multiplying the generation time by four and adding 1 hour.

The generation-times of the bacteria commonly encountered in clinical routine are according to Topley and Wilson's textbook (9) as follows:

Salmonella, Proteus	20—30 min.
Staphyloc., Streptoc.	25—35 »
Pseudomonas	30—40 »
Corynebact.	35—40 »

This means that the critical times with which we are concerned here will be 2.3, 2.6, 3.0, 3.3, and 3.7 hours. The results of our calculations based on these lines may be read from the following table, which is the basis of all diffusion graphs employed in this paper.

Table II.

Concentrations of antibiotic (σ) at distance (r) from diffusion centre. Calculated for $M = 5$ mg and for $M = 2$ mg.

N. B. The corresponding values for $M = 50$ I. U. (in the case of penicillin) are found by multiplying the values for $M = 5$ by factor 10 and by changing mg into I. U.

M = 5 mg (Land's tablets for streptomycin, aureomycin, chloromycin, terramycin)	Generation time (G. T.) in min.	Critical time (t) in hrs	1.6	1.7	1.8	2.0	2.2	2.5	2.8	Diameter of inhibition zone in cm	Distance (r) from centre of diffusion in cm	Concentration (σ) of antibiotic at distance (r) from centre in μ g/ml
			0.8	0.85	0.9	1.0	1.1	1.25	1.4			
			35	—	6.5	0.6	0.06	—	—			
	20	2.3	35	—	6.5	0.6	0.06	—	—			
	25	2.6	63	28.1	11.8	1.7	0.5	0.006	—			
	30	3.0	165	—	38	14.3	1.47	0.07	0.003			
	35	3.3	210	120	60	13.7	3	0.2	0.01			
	40	3.7	350	243	108	33.8	7	1.86	0.03			

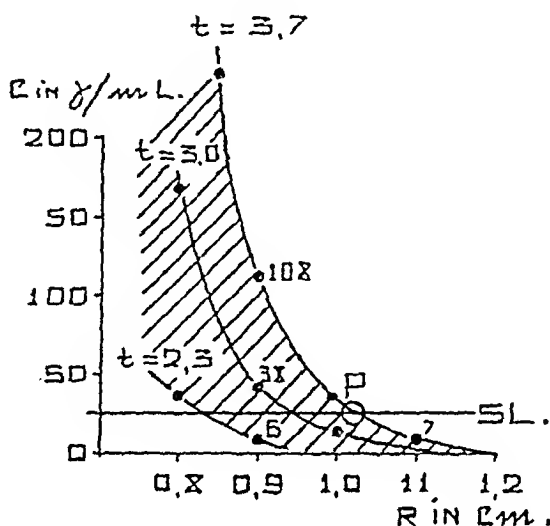
M = 2 mg (Land's tablets for sulphadiazine)	Generation time (G. T.) in min.	Critical time (t) in hrs	1.6	1.7	1.8	2.0	2.2	2.5	2.8	Diameter of inhibition zone in cm	Distance (r) from centre of diffusion in cm	Concentration (σ) of antibiotic at distance (r) from centre in μ g/ml
			0.8	0.85	0.9	1.0	1.1	1.25	1.4			
			14	—	2.6	0.02	—	—	—			
	20	2.3	14	—	2.6	0.02	—	—	—			
	25	2.6	24.2	11.3	4.7	0.68	0.2	0.002	—			
	30	3.0	66	—	15.2	5.7	0.56	0.025	0.001			
	35	3.3	84	48	24	5.46	1.2	0.63	0.004			
	40	3.7	140	97	43.2	13.5	2.5	0.74	0.02			

Since all the generation-times of the bacteria found in routine determinations are apt to vary between 20 and 40 minutes, we have, with an eye to our further considerations, found it useful to replace the bundle of lines, gained by this procedure, by an r-c area, lying between the line drawn for a generation-time of 20 min. ($t = 2.3$), and the line drawn for a generation-time of 40 min. ($t = 3.7$).

The shadowed area now represents the relationship between the inhibition zone and the m. i. c. for most of the common bacteria, given a certain fixed amount (in this case 5 mg) of antibiotic, placed at the centre of diffusion.

The significance of the horizontal line SL in our graph 2 will be explained in the following section.

Graph II.



$r-c$ lines drawn for critical times $t = 3.7, 3.0$ and 2.3 . The shadowed area between $t = 3.7$ and $t = 2.3$ comprises the $r-c$ lines, which can be constructed for all generation times between 20 min. and 40 min.

This graph has been constructed for an amount of 5 mg of antibiotic placed at the diffusion centre. (For further explanation see text.)

The Serum level of antibiotics.

If we want now to gain an impression of the chances of therapy with a certain antibiotic, by reading inhibition zones, we proceed as follows:

At the level of the concentration of antibiotic, generally reached in the serum after the normal dosage, we draw a horizontal line: «the serum level» (marked SL in our graph 2).

Let us suppose, that a streptomycin tablet, containing 5 mg of the antibiotic is placed on an agar plate, inoculated with a certain strain. Let the inhibition zone, read after incubation, be 2.2 cm in diameter ($r = 1.1$).

We are then, with the aid of our $r-c$ graph (see graph 2), able to infer, that the m. i. c. of streptomycin for this bacteria will be:

7 γ /ml if the generation-time of the bacteria is 40 min.; its critical time therefore $t = 3.7$ hours.

1.5 γ /ml if the generation-time of the bacteria is 30 min.; its critical time therefore $t = 3.0$ hours.

0.06 γ /ml if the generation-time of the bacteria is 20 min.; its critical time therefore $t = 2.3$ hours.

Let the expected serum level be 25 γ /ml (in actual fact this level is achieved with a daily dosage of 3 g). We then draw our serum level at 25 γ /ml. It is readily seen, that even for a generation-time of 40 min. ($t = 3.7$) the m. i. c. of streptomycin for the bacteria under study is below the serum level and the outcome of therapy will be favourable.

If the inhibition zone had been 1.8 cm in diameter ($r = 0.9$), then the m. i. c. of streptomycin for this bacteria would have been (see graph 2):

108 γ /ml if the generation-time of the bacteria is 40 min. ($t = 3.7$).

38 γ /ml if the generation-time of the bacteria is 30 min. ($t = 3.0$).

6.5 γ /ml if the generation-time of the bacteria is 20 min. ($t = 2.3$).

With a serum level of 25 γ /ml this would mean, that, in case the generation-time of the bacteria is 30 min. or 40 min. (critical time $t = 3.0$ or $t = 3.7$), the m. i. c. required, falls above the serum level and the success of therapy is doubtful.

From this example it will be clear, that to the right of point P, where the serum level cuts the r-c line drawn for $t = 3.7$ hours, all the m. i. concentrations (represented by our shadowed r-c area) fall below the serum level. This means, that for an inhibiting zone larger in diameter than the abscissa (r-axis) of point P, we may assume that the m. i. c. required for bacteriostasis, is below the serum level reached and the prognosis for our therapy with the antibiotic is favourable.

From the literature pertaining to this subject (6, 7) and from data gained in our clinics we compiled the following table, showing the serum level of different antibiotics, to be expected after certain common dosages of antibiotics.

We have constructed our r-c graphs for the Lund-tablets used in our clinics and have drawn the horizontal line of the serum level for the expected serum, levels according to the table shown above. It appears then, that inhibition zone an of more than 25 mm in diameter justifies a favourable prognosis of antibiotic therapy. If on the other hand the inhibition zone is smaller than 25 mm in diameter, we see, that most of the m. i. c.'s, represented by the shaded area, fall above the serum level and bacteriostasis is not to be expected. This appears to be very well in accordance with the experimental results, gained by Lund, Funder-Schmidt a. o. (2).

Table III.

Serum level of antibiotics occurring with usual dosage.

Antibiotic:	Sulpha	Penic.	Strepton.			Terram.			Chloramph.			Aureom.		
Dosage in g. daily (I. U. daily)	4	1 inj. of 100 000 I-II	1	1-2	3	1	2	4	1	2	4	1	2	4
Serum level in γ /ml (I. U./ml)	30-70	After 4 hrs. 0.2-2	2-5	10-20	20-40	1-2	2-3	5-6	2-3.5	1-6	2-14	1.5-2.5	2.5	1-4

Summary

This paper deals with an attempt to correlate the in-vitro results obtained by sensitivity testing of bacteria, according to Lund's method, with the serum level of the antibiotics required for adequate therapy.

By means of theoretical reasoning along the lines of Humphrey's general theory of plate assays, we tried to express the inhibition zone obtained by diffusion of a certain fixed dose of antibiotic in an inoculated agar plate, in terms of the minimum concentration, required for bacteriostasis in the common bacteria.

It appeared, that for the majority of bacteria, encountered in routine clinical testing, a favourable therapeutic result could be expected, if the inhibition zone shown, using Lund's tablets, was greater than 25 mm.

References.

1. Lund, E.: *Acta Path.* XXXI: 281 (1952). — 2. Lund and Funder-Schmidt: *Acta Path.* XXIX: 221 (1951). — 3. Cooper, K. E. and Gillespie: *J. Gen. Microb.* 7: 1 (1952). — 4. Cooper, K. E. and Linton: *J. Gen. Microb.* 7: 8 (1952). — 5. Humphrey and Lightbown: *J. Gen. Microb.* 7: 129 (1952). — 6. Bernstein, H. and Reber: *Schw. Med. Wo.* 81: 1 (1951). — 7. May and Morley: *Lancet* CCLXII: 636 (1952). — 8. May and Voureka: *B. M. J.* 1947, p. 627. — 9. Topley and Wilson: *Textbook of Bacteriology*.
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The So-Called «Dumping Syndrome» after Partial Gastric Resection for Peptic Ulcer.

By

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(Submitted for publication October 22, 1953.)

For some time in the literature the most frequently discussed postoperative complication of ulcer was undoubtedly the jejunal ulcer; but during recent years there has been a growing interest in the so-called «dumping syndrome». The fact that this syndrome, consisting of early postprandial complaints, was also found after gastro-enterostomy for peptic ulcer, appears in the earlier literature. Dénechaux (1) in 1907 described a well-defined syndrome after gastro-enterostomy: «syndrome dyspeptique secondaire à la gastro-enterostomie». Immediately after a meal the patient began to complain of feelings of pressure, borborygni and sometimes epigastric pain. In 1922 Mix (2) described a patient who had a gastro-enterostomy and on X-ray examination the barium meal was found to pass very rapidly through the stomach, soon arriving in the lowest part of the jejunum. This phenomenon was called by him «dumping stomach» quite independently of any connection with definite complaints. The appearance of symptoms on the one hand and the X-ray finding of rapid gastric evacuation on the other hand, gave rise to the term: «dumping syndrome».

In the literature the authors are unanimous as to the symptomatology of this syndrome *i. e.* subjective symptoms starting immediately after a meal and lasting about 20—30 minutes. Usually the symptoms begin 10—14 days after the operation. The frequency after gastric resection is stated to be from 14—75 %. The aetiology remains a point of discussion.

In a thesis presented in the University of Groningen (supervisor: Prof. Dr F. S. P. van Biehem) we discussed the results of a follow-up examination in 200 persons who had had operative treatment (100 by the method of Billroth I (gastroduodenostomy) mostly with Schoemaker's modification and 100 by the method of Billroth II (gastrojejunostomy) some with the modification of Polya-Reichel, some with that of Hofmeister-Finsterer).

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In all cases $3/5-2/3$ of the stomach was resected. 191 patients had been operated on for non-malignant ulcer, and 6 patients for gastritis. The interval between the operation and the re-examination was at least 5 years; in 60 % of the cases it was 6 or 7 years. The cases consisted of 187 men and 13 women. The ratio between partial gastrectomy for duodenal ulcer and that for gastric ulcer was 7 : 2. The average duration of the ulcer symptoms before operation was 9.5 years. All patients personally attended the outpatient department for examination.

From the histories it can be shown that the so-called «dumping syndrome» occurs in 65 % of the cases after Billroth I operation and in 88 % after Billroth II operation. As to the symptomatology of the syndrome, our findings are in accordance with those described in the literature.

The symptoms start very soon after the operation, usually after 10—14 days. They appear during, or straight after a meal, and last usually 20—30 minutes, and are of subjective nature: nausea, weakness, lassitude, a leaden feeling in the legs, accompanied by a desire to lie down, cold sweat on the forehead, a sensation of warmth and/or chilliness, sometimes flushings and a feeling of distension in the upper abdomen. Less frequently: dizziness, headache, palpitations, dullness, yawning and tremors, borborygmi and diarrhoea. A carefully organised history is necessary as the patients do not discuss their complaints spontaneously.

Whilst the immediate cause of the syndrome is a point of discussion in the literature, after accurate history-taking it appears that especially boiled whole milk food (whole milk porridge and milkpudding) or a glass of milk, may cause «the dumping syndrome». The complaints appear especially when the patient takes whole milk food after a meal. Fatty foods, pulses, cabbages, unpeeled fruits and coffee are generally well-tolerated. The intensity and the duration of the complaints decrease in the recumbent position though this does not prevent their appearance. In most cases the sensations are different from those which occur after a full meal.

The symptoms do not resemble those of peptic ulcer; the pain is absent in the syndrome; this is an essential difference from the history of post-operative peptic ulcer.

Most investigators (3—12) attach great value to the rapid emptying of the gastric remnant in explaining the early postprandial complaints. It is especially the radical anatomical alterations rather than the functional changes caused by the operation which have been connected with the syndrome disorders following. In an investigation as to whether any relationship exists between the early postprandial complaints and the rapid emptying of the gastric remnant X-ray examination of the upper gastrointestinal tract provides an excellent means of study. After administration of the barium meal it is possible to see the details of the gastro-intestinal tract. Only after this examination can we estimate whether the so-called «dumping syndrome» does indeed depend on a «dumping» of the gastric contents into the small intestine.

93 of the 100 patients operated upon by the method of Billroth I were X-rayed and 90 of the 100 patients operated on by the method of Billroth II type of resection. Primarily we noted the gastric emptying-time. We can speak of «dumping» when the evacuation of a 150 cc barium meal takes place within 10 minutes. This

was the case in 52 % of the Billroth II stomachs compared with 14 % of the Billroth I stomachs. We very often gained the impression that the Billroth II stomachs showed a gastric stump which was merely an elongation of the oesophagus. The emptying of the stomach in the Billroth I group took place within 20 minutes in 35 % of the cases as compared with 82 % of the Billroth II group. Considering the speed of emptying in relation to the appearance of the early postprandial complaints, it seems that there is no connection between the speed of gastric evacuation and the syndrome.

After systematic questioning it appeared that whilst standing in front of the screen, none of the patients with a «dumping» stomach had any symptoms, not even those with the so-called «dumping-syndrome». This is in contrast to the finding of Butler and Capper (13) who found typical symptoms during X-ray examination in 79 % of the Billroth II resections. They never found the syndrome after Billroth I resection.

The other X-ray findings in the operated stomachs, the type of evacuation, the estimated volume of the gastric stump, the presence of a pseudo-pylorus function in the Billroth I stomach and the formation of an «after stomach» in the efferent jejunal loop after the Billroth II resection, were not connected with the occurrence of the syndrome.

The following is a short review and criticism of the different theories in the literature:

1. *The sudden mechanical distension of the upper small intestine by the dumping of food is not an adequate explanation for the symptoms. For the following reasons this theory is not primarily the cause of the syndrome:*

- a) The results of the X-ray examination mentioned above.
- b) A detailed history of the digestion shows that liquid food such as soup (which distends the small intestine all at once) was well tolerated by 95 % of the operated patients.
- c) A group of 9 persons with an intact gastro-intestinal tract and a group of 4 persons after partial gastrectomy were submitted to an experimental distension of the upper small intestine by rapidly inflating the balloon of a Miller-Abbott tube (approximate pressure of 50 cms of water on the enteric wall).

None of these persons taking part in the experiment had any complaints comparable to those of the so-called «dumping-syndrome».

The opinion of Machella (12), like that of Kirkebey (15), which postulates that the mechanical distension of the small intestine is a result of the osmotic action of hypertonic foodstuffs is not supported by the gastric findings. From operated patients 80 glucose tolerance curves were prepared after taking 200 cc 25 % glucose or 200 cc 25 % lactose. None of the patients complained after having taken the concentrated sugar solution. Milk and porridge which are certainly not more hypertonic nevertheless do cause complaints.

2. French investigators (16, 17) suppose the cause to be greatly *diminished capacity of the resected stomach: «syndrome du petit estomac»*.

It appears indeed that 60 % of the operated patients cannot tolerate large meals. The subjective complaints however differ in the lack of vasomotor symptoms from

those of the so-called «dumping syndrome». During X-ray examination special attention was given to the size of the gastric stump in relation to other early postprandial complaints in the history. Between those no statistical correlation was found.

3. One author (18) suggests that there is a so-called *hyperglycaemic shock*. We did not notice any symptoms during the hyperglycaemic phase of the glucose tolerance curves in patients after gastric resection. The blood pressure and pulse rate taken during the period of subjective symptoms show no signs of shock either.

4. Some authors (19, 20, 21) believe that *alimentary hypoglycaemia* is responsible for the syndrome. An essential difference exists between the late postprandial syndrome, the symptoms of which are due to hypoglycaemia $1\frac{1}{2}$ —3 hours after the meal and the early postprandial symptoms or the so-called «dumping syndrome» appearing immediately after food intake. Only the latter is dealt with in this article.

The glucose tolerance curve after gastric resection shows the form of a *slag* curve: i. e. an early high peak, followed by a rapid fall. Table 1 shows that there is no correlation between the intensity of the dumping syndrome and the highest and lowest values of glucose, estimating the blood sugar value, every 15 minutes during three hours.

Table 1

The so-called «dumping syndrome» and the highest and lowest values in the glucose tolerance test.

Severity of so-called dumping syndrome	Number of cases	Average of maximal blood sugar value	Average of minimal blood sugar value
severe	12	218 mg %	66 mg %
slight	11	194 mg %	64 mg %
absent	3	169 mg %	67 mg %

Analysis of the tolerance curves after ingestion of 50 gr lactose and 250 cc porridge in relation to the occurrence of the early postprandial syndrome showed no constant relationship between the two.

5. Other authors (22—29) ascribe the syndrome to *gastritis*, especially at the site of the anastomosis. Experienced users of the gastroscope find signs of inflammation in nearly every stomach after operation. The symptoms of gastritis differ however from those of the so-called «dumping syndrome», and the patients with gastritis tolerate milk-foods very well.

6. Porges (30) follows on the same lines when he speaks of the *jejunal syndrome* caused by *postoperative jejunitis*. He has also observed the syndrome in persons who have had no operation and who are suffering from enteritis.

7. A disturbance in *mineral metabolism* is also suggested in conjunction with the syndrome. Jasinski and Ott (31) consider an iron deficiency to be one of the causal factors of the syndrome. In our investigation, however, no connection was found

between the symptoms and the presence of hypochromic anaemia, which may develop in operated patients through an iron deficiency.

In fact a slight hypochromic anaemia (Sahli value between 70–80 % and R. B. C. 4–4.5 millions/mm² for men and respectively 60–70 % and 3.5–4 millions/mm² for women) was found in 12 % of patients after gastric resection (179 persons). Only one woman, operated upon at the age of 37, had a marked hypochromic anaemia, Sahli 46 %, R. B. C. 2,420,000. Hamilton Smith (32) found a shortage of potassium in patients after gastrectomy and suggests it to be of possible significance in causing the early complaints. This does not explain the finding that it is precisely milky foods, which are rich in potassium, that give rise to the symptoms.

8. We think that *achlorhydria* in the stomach after operation is an important factor in the origin of the so-called «dumping syndrome». In the normal stomach hydrochloric acid and pepsin, probably in the form of lebferment or rennin, have a very important function in the digestion of milk. In acid media the casein of the milk is changed by the pepsin into paracasein, and in the presence of calcium ions the paracasein begins to clot. This process is called curdling of the milk. As a rule the gastric stump secretes neither pepsin nor hydrochloric acid, so that the milk proteins, in part also because of the increased speed of passage of the gastric contents, reach the small intestine unchanged. When in infants the stomach of the child is incapable of digesting the relatively large quantities of milk, sour milk products are recommended. This has the advantage that for the neutralization of the milk, no extra hydrochloric acid is necessary. Moreover the casein is already finely precipitated before the food mass arrives in the stomach. Thus the stomach is relieved, the enteric enzymes can digest the casein much better and the intestinal flora is favourably influenced.

In the course of the investigation special attention was paid to the quality of the milk in cases where it was not well tolerated. It appeared that ordinary cowsmilk especially and whole milk porridge gave rise to symptoms. Sour milk products as buttermilk and yoghourt were usually well tolerated. 67 % of 135 operated ulcer patients with the «dumping syndrome» therefore who did not tolerate whole milk products, could tolerate sour milk products very well, compared with 14 % who could not and 19 % who were incapable of giving an answer as they had not taken these foodstuffs after operation.

9. A second important theory is that of enteric intoxication which includes also that of *alimentary allergy*. Through the insufficiency of the motor and secretory gastric functions the milk proteins enter the small intestine in an unprepared state. The latter is inundated with undigested milk proteins and it is probable that the intestinal enzymes (trypsin) cannot split them satisfactorily. Resorbable amino-acids are incompletely formed, and it is suggested that partially digested milk proteins are absorbed. The particular conditions of absorption in the small intestine after gastric resection may give rise to sensitisation to the various food-stuffs *i. e.* milk.

In this sense the so-called «dumping syndrome» can be considered to be an allergic phenomenon. Usually the symptoms start 10–14 days after the gastric resection, which rather favours the theory of allergic origin. Moreover, sometimes chocolate

and egg as well as milk are badly tolerated in the same way. 70 operated patients, all with the so-called «dumping syndrome» were submitted to allergic skin tests with extracts of cocoa, oatmeal, cornflour and milk — the latter three articles of food being the ingredients of pudding and porridge which cause the so-called «dumping syndrome». As a control, to evaluate the skin tests, 62 voluntary patients from the ward were tested; of these none had registered any complaints to indicate that they could not take certain foodstuffs. The ratio of the percentages of positive skin reactions in 70 operated patients with the so-called «dumping syndrome» compared with 62 control patients was 56 : 75 for cocoa, 64 : 24 for oatmeal, 39 : 23 for cornflour and 50 : 21 for milk. With the help of statistical analysis the differences appear to be significant as regards the positive results of the skin reactions for oatmeal, cornflour and milk. These facts may support the view of an allergic origin of the so-called «dumping syndrome».

10. It is an old finding that in «ulcer diseases» the *psyche* plays an important rôle. Resection interferes with only one, be it important, symptom of this disease. Many operated patients declared, that the complaints of the so-called «dumping syndrome» were most troublesome when they were feeling «wound-up» because of their work. The fact that it is a general finding that frequently the syndrome is not felt in hospital or during periods of rest, favours a psychical influence.

It is known also that the *psyche* can influence the excitation level of the autonomic nervous system.

11. We now discuss the difficult problem of *lability of the autonomic nervous system* in connection with the «dumping syndrome». In all our 200 resected patients we determined the blood pressure, the pulse rate (lying and standing), the respiratory rhythm, whether dermatographia was present and also tested the intensity of the reflexes. There was however no connection between the so called «dumping syndrome» and these clinical indications of a labile autonomic nervous system. This constitutional inferiority can however be of great importance in the development of allergic symptoms.

The significance of both the latter factors is also apparent from an investigation into the occurrence of ulcer sufferers in the family of the operated patients. This suggests that a constitutional factor very probably plays a part in the aetiology of peptic ulcer. Of the operated cases exhibiting the so-called «dumping syndrome» in 63 % there were ulcer cases in the family, whilst in only 36 % of the cases without the so-called «dumping syndrome» was a positive family history found. The difference is statistically significant, the chance of its being incidental is 0.1 %. In persons who after operation have developed the so-called «dumping syndrome» the constitutional factor is more important than in the post-operative group without the so-called «dumping syndrome». This constitutional factor can show itself in the autonomic nervous system, in the *psyche* and the allergic state.

To summarize: the coincidence of the following factors may be responsible for the so-called «dumping syndrome»:

¹ Although it is known that skin tests have a relative value only in the demonstration of elementary allergy, statistical comparison of results obtained may give a general conclusion as to its presence, rather than in any individual case.

- 1) the absence of pepsin (and/or renin) and hydrochloric acid
- 2) the accelerated gastric emptying
- 3) the allergic condition of the gastro-intestinal tract.

The pathogenesis of the so-called »dumping syndrome» may be summarized as follows:

- 1) The »dumping syndrome» can probably be regarded as an allergic phenomenon.
- 2) Partially digested milk proteins could act as antigens
- 3) These may arise from the defective digestion of milk proteins
- 4) The incomplete digestion is caused just as much by the accelerated gastric evacuation as by the lack of pepsin and hydrochloric acid in the gastric stump.

It appears from the preceding considerations that the so-called »dumping syndrome» may be a result of the changed motor and secretory functions of the gastro-intestinal tract, following gastric resection. The »dumping syndrome» must be accepted as an inevitable post-operative following in most cases. A Billroth I resection gives the least chance of the symptom complex and in this operation also, the severity of the complaints is less than after a Billroth II resection.

Treatment is usually not necessary as the complaints are so slight in most cases that the patient does not consult a doctor. As a rule the patient learns to prevent the symptoms by avoiding the foods he cannot tolerate.

The following scheme of treatment is recommended:

- 1) Avoidance of foods which may give rise to symptoms. This usually means whole milk foods.
- 2) Replacement of these foods by sour milk products.
- 3) The assumption of a recumbent position on the appearance of the symptoms.
- 4) Should the above-mentioned suggestions fail to give relief, anti-allergic therapy can be considered:
- 5) Where the symptoms are very serious another laparotomy should be considered in order to change the Billroth II into a Billroth I anastomosis. (Bohmanson (33).)

Summary.

In order to analyse the early postprandial complaints of patients who have undergone a partial gastric resection, a follow-up examination was made 5 or more years after the operation. The so-called »dumping syndrome» occurred in 65 % of the 100 patients after Billroth I operation and in 88 % of the 100 patients after Billroth II operation. Whole milk food especially (milk porridge, milk pudding) seemed to cause the syndrome, while conversely sour milk products were well tolerated.

The different theories of the aetiology of the syndrome are discussed in the preceding paper. No support is given to the theory of the sudden mechanical distension of the upper small intestine giving rise to the »dumping syndrome». It is felt that hypofunction of the operated stomach: achlorhydria and accelerated gastric emptying may be responsible for the disturbed digestion of proteins.

Finally the syndrome may be considered as a manifestation of alimentary allergy.

References.

1. Dénéchaux: Thèse, Paris 1907. — 2. Mix, C. L.: S. Clin. North. Amer. 2: 617, 1922. — 3. Hertz, A. F.: Ann. Surg. 58: 466, 1913. — 4. Schwartz, A., Reingold, I. and Necheles, H.: Am. J. Digest. Dis. 9: 151, 1942. — 5. Custer, M. D., Butt, H. R. and Waugh, J. M.: Ann. Surg. 123: 410, 1946. — 6. Berkman, J. M. and Heek, F. J.: Gastro-enterology 5: 85, 1945. — 7. Irvine, W. T.: Brit. Med. J. 2: 514, 1948. — 8. Steinberg, M. D.: S. G. O. 88: 453, 1949. — 9. Hoffmann, V.: Münch. med. Wchnschr. 86: 332, 1939. — 10. Hoffmann, V.: Arch. f. klin. Chir. 195: 312, 1939. — 11. Boller, R.: Der operierte Magen. Urban und Schwarzenberg, Wien 1947. — 12. Machella, T. E.: Gastro-enterology 14: 237, 1950. — 13. Capper, W. M. and Butler, T. J.: Brit. Med. J. 4726: 265, 1951. — 14. Welbourn, R. B., Butler, T. J. and Capper, W. M.: Proc. roy. Soc. Med. 44: 773, 1951. — 15. Kirkeby, A. V.: Nordisk Med. 18: 671, 1951. — 16. Sènèque, J.: L'avenir des gastrectomisés. Fießinger, N.: Les maladies actuelles: 155, Masson et Cie, Paris 1942. — 17. Gutmann, R. A.: Les syndromes douloureux de la région épigastrique. 2. G. Doin and Cie, Paris 1947. — 18. Glaessner, C. L.: Am. J. Digest. Dis. 12: 157, 1945. — 19. Gilbert, J. A. L. and Dunlop, D. M.: Brit. med. J. 2: 330, 1947. — 20. Lake, N. C.: Brit. med. J. 1: 285, 1948. — 21. Barnes, C. G.: Lancet 2: 536, 1947. — 22. Konjetzny, G. E.: Der Chirurg 4: 402 and 433, 1932. — 23. Henning, N. and Baumann, W.: Lehrbuch der Verdauungskrankheiten. Georg Thieme, Stuttgart 1949. — 24. Morawitz, P.: Der Chirurg 4: 265, 1932. — 25. Wanke, F.: Münch. med. Wchnschr. 77: 198, 1930. — 26. Friedrich, L. von: Gastro-enterologia 69: 286, 1944. — 27. Berg, H. H.: Der Chirurg 4: 318, 1932. — 28. Kalk, H.: Der Chirurg 8: 381, 1936. — 29. Schindler, R.: Am. J. Digest. Dis. 7: 505, 1940. — 30. Porges, O.: Am. J. Med. 3: 177, 1947. — 31. Jasinski, B. and Ott, W.: Schweiz. med. Wchnschr. 81: 1141, 1951. — 32. Hamilton Smith, W.: Lancet 6687: 745, 1951. — 33. Bohmansson, G.: Acta med. Scand. suppl. 246: 37, 1950.
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Die Exspirationskurve der Vitalkapazität, ihre Auswertung und Verwendung.

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Die Messung der Vitalkapazität (VK) ist eine der ältesten Methoden, die zur Begutachtung der mechanischen Ventilationskräfte gebraucht wird. Durch Auswertung des zeitlichen Verlaufes der forcierten Ausatmung der VK wird diese einfache Methode viel brauchbarer, da man die Ausatemungskräfte der Lunge dynamisch auswerten kann. Es ist ganz klar, dass je grösser die VK ist und je kürzer die Zeit, die zu ihrer Ausatmung nötig ist, desto besser ist die mechanische Funktion der Lungen. Eine kleine VK, die nur langsam ausgeatmet werden kann, ist ein Zeichen, im Gegenteil, einer schlechten Funktion. Nach diesen Grundsätzen werden auch andere Lungenfunktionsprüfungen, wie z. B. die Messung des Maximalenminutenvolumen, der Atmungsreserve und der Spiromanometrie ausgearbeitet. Alle diese Methoden vermissen aber die Möglichkeit einer Kontrolle, sind wenig objektiv, so wie die allgemeine Messung der VK.

Unsere neue einfache Methode begutachtet zwar nur die Ausatemungskräfte der Atmungsorgane, dies ist aber kein grosser Nachteil, da beinahe alle Erkrankungen, die die mechanischen Ventilationsfunktionen benachteiligen, die Exspirationskräfte mehr als die Inspiration befallen. Auch Raither (1), der die Kurven bei Atmung der VK im geschlossenen System begutachtet, sah, dass in pathologischen Fällen immer mehr die Expiration als die Inspiration befallen ist.

Das von uns benutzte Instrument besteht aus einem üblich gebrauchten Hutchinsonschen Spirometer mit möglichst leichten beweglichen Teilen, die mit einer Registrationsvorrichtung eines mechanischen Kymographen verbunden sind, so dass man bei Ausatmung der VK eine Kurve auf dem Kymographen schreiben kann. Das Papier des Kymographen bewegt sich mit einer Geschwindigkeit von 55 mm/Sek., so dass man leicht auch 1/10 Sek. ablesen kann (Abb. No. 1). Die untersuchte Person vordert man auf womöglich tief einzusatmen und bei geschlossener Nase (mit der üblichen Klammer) alle Luft womöglich schnell in den Spirometer

zu blasen. Der Grossteil der Untersuchten begreifen dies ohne Schwierigkeiten, nur hie und da ist eine Instruktag mit mehreren Versuchen nötig. Bei gutem Willen des Untersuchten sind dann zwei mit kurzer Pause nacheinander geschriebene Kurven völlig identisch. Dadurch können wir auch jegliche Simulation ausschliessen. Durch Eigenversuche haben wir uns überzeugt, dass es bei absichtlich gehemmter Atmung nicht gelingt zwei identische Kurven zu schreiben. Die Ausatemungskurve ist für einzelne Personen charakteristisch und ändert sich lange Zeit nicht, zuweilen es zu keiner Änderung der mechanischen Lungenfunktion kommt. Diese Methode eignet sich darum zu Begutachtungszwecken, denn bei diesen Fällen müssen wir mit einer Psychose, Simulation oder Aggravation, rechnen.

Bei Vergleichen unserer Kurven der ausgetmeten VK mit anderen Funktionsprüfungen und dem klinischen Bilde der Untersuchten sahen wir, dass für die Auswertung nicht nur die Höhe der Kurve und die Ausatemungszeit, sondern auch ihre Form von grosser Bedeutung ist. Bei gesunden Personen bekamen wir Kurven, die steil und bis zu $\frac{2}{3}$ der VK in einer geraden Linie verlaufen. Erst nach der Ausatmung von $\frac{2}{3}$ der VK beginnt die Schnelligkeit des Luftstromes abzufallen und die Kurve rundet sich ab, erreicht auch ihr Ende mit einem weit milderen Gefälle als am Anfang (Abb. No. 2). Da das Ende der Kurve meistens durch Expression mit Hilfe der Bauchmuskulatur deformiert ist, ist es möglich, bei ihrer Auswertung nur ihren Anfang zu benützen. Die Kurve ist an ihrem Ende auch bei gesunden muskulären Personen enorm protrahiert.

Bei Änderungen im Lungenparenchym und in den Luftwegen ändert sich die Form der Kurve, meist, wie wir weiter zeigen wollen, in einer ganz typischen Weise. Änderungen der Elastizität des Lungenparenchyms der Atemmuskulatur, der Beweglichkeit des Brustkorbes (im Sinne einer entstehenden Rigidität) so wie auch Hindernisse, die der ausgetmeten Luft in den Luftwegen im Wege stehen, machen sich meist in der Form der Ausatemungskurve der VK charakteristisch kennbar. Je nachdem, wie weit diese Komponenten der mechanischen Atmung angegriffen sind, kommt es zu einer geringeren oder stärkeren Verlangsamung des Atemungsluftstromes.

Bei einem Emphysem, welches durch Verlust an Elastizität des Lungengewebes charakterisiert ist, wo die Ausatemungskräfte auch noch durch einen rigiden Brustkorb beeinträchtigt sind, ist die Ausatemungskurve der VK schon an ihrem Anfang flach und verliert in ihrem weiteren Ablaufe immer noch an Gefälle (Abb. No. 3 und 4). Bei überwiegender Bronchitis, wo das Lungenparenchym noch nicht geschädigt ist, die Luftwege aber etwas eingengt sind, sieht man an der Atemungskurve eine Verlangsamung des Atemungsluftstromes, aber die Krümmung der Kurve liegt niedriger (Abb. No. 5). Bei Bronchialspasmus sehen wir oft wellenartig ablaufende Kurven mit kleiner Ausatemungsgeschwindigkeit. Diese Erfahrungen führten uns zu folgender Auswertungsmethode der Kurven, welche nach der angeführten Formel einen Index der VK bestimmt (weiter unter I_{VK}):

$$I_{VK} = 2 \cdot \frac{VK}{p} - \frac{VK}{p_{VK}} - t$$

VK = Vitalkapazität in Liter

p = Körperoberfläche in m²

pVK = so genannte partielle Vitalkapazität in Liter, d. h. jene Menge der ausgeatmeten Luft, die die untersuchte Person von Anfang der Ausatmung mit gleicher Schnelligkeit ausatmet. Praktisch ist das jener Teil der Ausatemungskurve, welcher in einer geraden Linie verläuft

t = die Zeit in Sek., die zur Ausatmung eines Liters der VK gebraucht wird.

Den Wert der pVK (partielle Vitalkapazität) lesen wir von der Kurve so ab, dass wir von der Abszisse durch die Kurve von Anfang eine gerade Linie ziehen und dort, wo die Kurve von dieser Geraden abweicht, endet dann die pVK. Ein Beispiel des Ablesens der zur Berechnung des Indexes der VK nötigen Werte bringt die Abb. No. 2.

Bei Berechnung des I_{VK} ist es auch auf die Körperoberfläche Rücksicht zu nehmen um individuelle Schwankungen der Konstitution womöglich auszuschalten. Der numerische Wert des Indexes ist grösser, je grösser die korrigierte VK und je kleiner das Verhältnis VK/pVK und kürzer die Zeit »t« ist. Je grösser der I_{VK} , desto besser die Funktion der mechanischen Ventilation der Lunge.

Roche und Thivollet (2) benützen zur Begutachtung der Lungenfunktion eine ähnliche Methode; zur Auswertung benützen sie aber nur die Litration der VK, welche in einer Sekunde ausgeatmet werden kann. Durch die ebenangeführte mathematische Auswertung erreichen wir aber eine feinere Differentiation der verschiedenen Formen der Ausatemungskurven (Abb. No. 6). Beide Kurven, A und B, stellen eine gleiche VK vor, welche aber auf verschiedene Art erreicht wird. Durch die Auswertung nach Roche und Thivollet sind die mechanischen Lungenfunktionen beider Versuchspersonen nach deren Kurven A und B gleichwertig. Nach unserer Auswertung finden wir aber bei der Kurve A einen Index $I_{VK} = 0.0$, bei der Kurve B gleicht der $I_{VK} = + 0.4$. Wir betrachten danach die Lungenfunktion der Versuchsperson A mehr beschränkt als die der Person B; dies stimmt auch mit unseren pathophysiologischen Vorstellungen überein, welche uns die Praxis mit dieser Methode und Begutachtungen der Kurven gezeigt hat. Die Kurve A zeigt ein Bild von Verlust an Elastizität des Lungengewebes im Sinne eines Emphysems, das Bild B ein Hindernis in den grösseren Luftwegen. Es ist auch bestimmt ein Verlust an Elastizität des Lungengewebes, welches eine irreversible Änderung des Lungenparenchyms vorstellt, als ein ernsterer Gesundheitsschaden zu betrachten, als z. B. eine Bronchitis. Weiter wollen wir noch bemerken, dass bei einer Auswertung nach Roche und Thivollet jener Teil des Ausatemungsmechanismus, welcher jenseits der ersten Sekunde liegt, nicht berücksichtigt wird.

Um sich besser orientieren zu können, bestimmten wir die Normalwerte durch Untersuchung 56 klinisch gesunder Personen in einem Durchschnittsalter von 46 ± 10 . Das arithmetische Mittel des I_{VK} ist bei dieser Norm $+ 2.0$ ($\sigma = \pm 0.46$). Wenn wir zur Abgrenzung der Normalwerte 2σ , wie üblich, gebrauchen und den Wert des berechneten σ von 0.46 auf 0.5 abrunden, müssen wir Werte des I_{VK} von $+ 1.0$ bis $+ 3.0$ als normal betrachten. Werte über $+ 3.0$ sehen wir dann bei Sportlern und abnormal entwickelten Menschen.

Durch Untersuchung von 1,300 Bergleuten, welche röntgenologisch keinen Lungenbefund hatten, konnten wir unsere oben angeführte Norm des I_{VK} ($= + 2.0$) im Durchschnittsalter von 45 Jahren als richtig finden, wie wir auch oben anführten.

Bei 20- bis 25-jährigen fanden wir einen I_{VK} von 2.5, bei 55- bis 60-jährigen war der Index gleich 0.8. Bis zu dem Alter von 45 Jahren verschlimmert sich der Index nach fünf Jahren im Durchschnitt um ungefähr 0.15, nach 45 Jahren fiel der Index steiler ab, und zwar in fünfjährigen Intervallen um einen Durchschnittswert von ungefähr 0.4.

II. Die Branchbarkeit dieser Methode wollen wir an einigen Beispielen den Lesern präsentieren.

Gute Dienste erwies uns diese Methode bei Entschädigung von Staublungen-erkrankungen der Bergleute, denn die Höhe der Rente richtet sich bei nicht komplizierten Formen der Silikose nicht nur nach dem klinischen Bild, sondern auch nach der Beeinträchtigung der Lungenfunktion. Wie wir oben angeführt haben, ist ein Durchschnitt des I_{VK} bei Untertagsarbeitern mit negativem Lungenröntgenogramm (die aber eine Rente erhalten) gleich 1.8, bei einer Gruppe mit dem Röntgenbild einer silikotischen Reticulation (Anfangsstadium) $+ 1.0$, bei kleinnodulärer Form von Silikose $+ 0.7$ und bei komplizierter Silikose $+ 0.0$.

Durch statistische Auswertung nach Fishers *st* Test kann man alle angeführten Gruppen mit dieser Methode von der Gruppe mit normalem Röntgenogramm und auch untereinander bei gleichem biologischen Alter differenzieren.

Die Methode des Maximalenminutenvolumen (MMV) und die der Bestimmung der Atmungsreserve konnten die oben angeführten Gruppen nicht differenzieren. Bei wiederholten Untersuchungen zeigte sich, dass die Methode des I_{VK} viel konstantere Resultate als andere Methoden gibt (Rejsek, 6).

Bei Untersuchung von Zementfabrikarbeitern, die an staubgefährdeten Arbeitsplätzen länger als sieben Jahren arbeiten, konnten wir bei einer Gruppe mit klinisch normalem Lungenbefund das arithmetische Mittel des I_{VK} gleich $+ 1.6$ finden. Bei Bronchitikern betrug dies $+ 0.8$ und bei Arbeitern mit Lungenemphysem $= - 0.3$.

Die Expirationskurve der Vitalkapazität ändert sich auch durch Kreislauf-erkrankungen, welche mit einer Lungenstauung begleitet sind. Einer von uns (5) konnte zeigen, wie man eine Kompensation bei kardiotonischer Behandlung durch diese Methode gut verfolgen kann. Besonders bei schwerer dekompensierter Mitralstenose mit grösserer Stauung im kleinen Kreislauf verbesserte sich der Index der Vitalkapazität während erfolgreicher kardiotonischer Behandlung erheblich, im Durchschnitt von $- 1.5$ auf $+ 0.1$. In zwei Fällen kardiotonischer Behandlung konnten wir mit Hilfe des I_{VK} eine Abnahme der Lungenstauung und eine Besserung der mechanischen Lungenfunktion feststellen, trotzdem, dass die Vitalkapazität gleich blieb (siehe Abb. No. 7 und 8). Es zeigte sich, dass der I_{VK} den Zustand der Stauungslunge viel besser nachweist, als die blosse Messung der Vitalkapazität. Bei kompensierter und dekompensierter Mitralinsuffizienz fanden wir im Durchschnitt höhere Werte des I_{VK} . Ein Patient mit dekompensierter Mitralinsuffizienz besserte seinen I_{VK} während der kardiotonischen Behandlung von

— 2.7 auf + 0.25. Nach zwei Monaten kam er wieder völlig dekompenziert ins Krankenhaus. Die Anfangswerte des I_{VK} waren gleich wie zum erstenmale; er erreichte wieder bei erfolgreich beendeter kardiotonischer Kur einen I_{VK} von + 0.25. Die Kurven waren in allen Phasen der Behandlung bei der ersten und zweiten Kur gleich (siehe Abb. No. 9).

Auch bei Behandlung von Herzmuskelschäden mit aktiven Herzglykosiden konnten wir eine Besserung des I_{VK} im Durchschnitt um 0.37 feststellen.

Die niedrigsten Werte des I_{VK} sahen wir bei dekompenziertem cor pulmonale chronicum. Hier muss man ausser der Stauung im kleinen Kreislauf auch die pathologischen Veränderungen im Lungenparenchym selbst in Rechnung ziehen. Der Durchschnittswert bei dieser Gruppe war — 8.7. Bei einer Kompensation wuchsen die Werte des I_{VK} enorm, im Durchschnitt um 6.5. Die Form der Kurve macht uns aufmerksam, dass es hier nicht nur um den kleinen Kreislauf, sondern auch um den Lungenparenchym selbst geht. Besonders typisch sind die Kurven der Emphysematiker. Die Abb. No. 10 zeigt die Kurve eines Patienten mit dekompenziertem arteriosklerotischem Herzmuskelschaden, eine andere eines Emphysematikers mit cor pulmonale. Beide Fälle weisen eine gleiche VK auf, doch ist der I_{VK} bei dem zweiten Fall weit schlechter, denn die Kurve krümmt sich schon an ihrem Anfang. Dies weist auch auf ein schweres Emphysem hin.

Sehr gute Dienste leistet diese Methode auch bei der Diagnostik eines Bronchialspasmus. Wir nehmen hier zwei Untersuchungen vor: die erste vor, die zweite nach einer Inhalation von einem bronchodilatatorischen Aerosol. Es ist zweckmässig diese Untersuchungen auch nach therapeutischer Aerosolbehandlung zu wiederholen. So kann man leicht die Erfolge, die uns die Patienten freudig melden, auf das Papier des Kymographen bringen (siehe Abb. No. 11). Man kann auch mit dieser Methode die sich steigernde Leistung des Atmungssystems bei Sportlern, die sich einem Training unterziehen, verfolgen. Auch konnte man mit dem I_{VK} die Besserung bei einer Methylthiouracilbehandlung bei Hyperthyreosen nachweisen.

Zum Schluss wollen wir noch bemerken, dass die Methode der Expirationskurve der Vitalkapazität bei Untersuchungen aller oben angeführten pathologischen Zustände gute Dienste leistet und brauchbarer als andere Lungenfunktionsprüfungen ist, denn sie ist einerseits einfach und schnell, belastet minimal den Patienten, andererseits informiert sie den Arzt genügend über das mechanische Ventilationsvermögen des Untersuchten.

Summary.

A method of registering graphically the vital capacity has been worked out. The resulting curves are evaluated by the index I_{VK} calculated from the values read from the curve and the body surface area. For a group of healthy persons of an average age of 46 years an index $I_{VK} = 2.0 \pm 0.5$ (1 σ) was established. The method was statistically evaluated by measurements conducted in miners with silicosis accompanied by simple bronchitis, and cement workers with bronchitis and emphysema, and is considered better than other spirometric and spirographie methods. It is also useful in eliminating intentional distortion

of the results in persons with indemnity claims. Clinically it is well suited as a diagnostic method. Cardiac compensation treatment, patients recovering from bronchitis and cases of toxic struma can well be followed by this method.

Bibliographie.

1. Raither, E.: Btr. klin. Tuberkul. 22, 151. — 2. Roche, L., Thivollet, J.: Arch. mal. prof. 10, 448, 1949. — 3. Kadlec, K., Vyskočil, J.: Prac. lék. 2, 1, 1950. — 4. Kadlec, K., Vyskočil, J.: Prac. lék. 2, 348, 1950. — 5. Vyskočil, J.: Lék. listy 6, 495, 1951. — 6. Rejsck, K.: Prac. lék. 4, 207, 1952.
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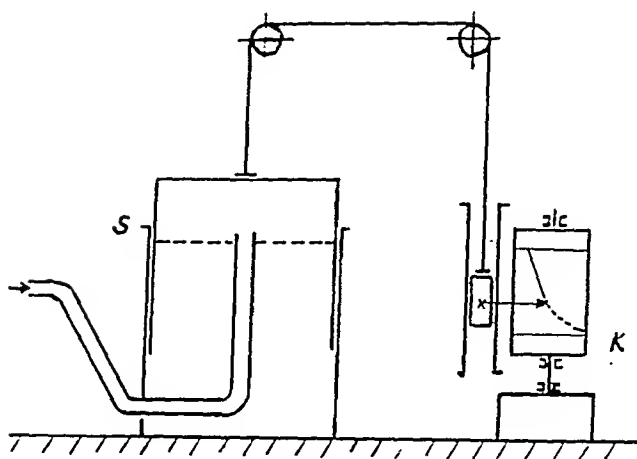


Abb. No. 1.

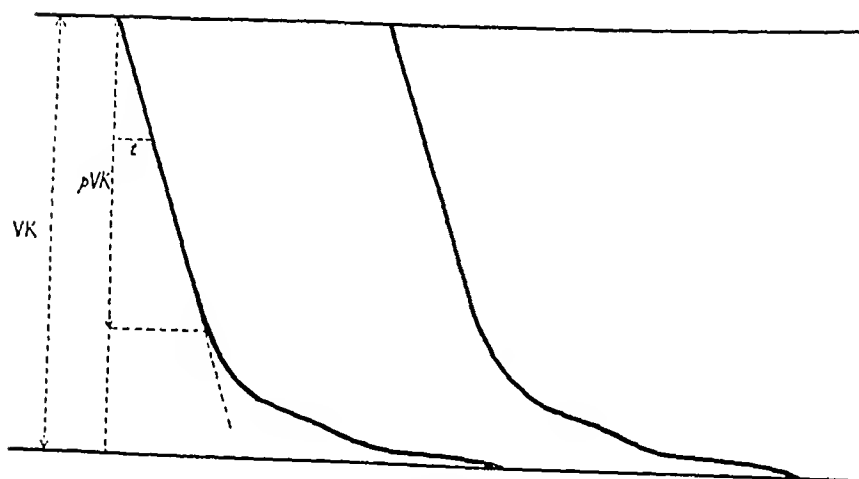


Abb. No. 2. $I_{VK} = 2 \frac{VK}{P} - \frac{VK}{pVK} - t = 2 \frac{4.1}{1.8} - \frac{4.1}{3.0} - 0.2 = 2.8$
 Ausatemungskurve eines Gesunden.

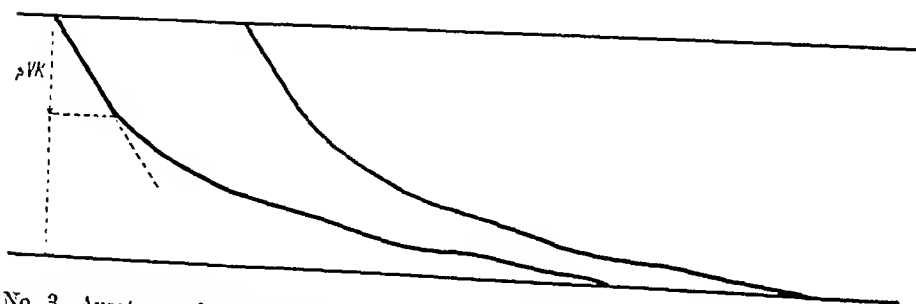


Abb. No. 3. Ausatemungskurve der VK eines Emphysematikers. C. J., 45 J., 162 cm, 57 kg; emphysema pulm. levioris gr. $I_{VK} = 0.0$.

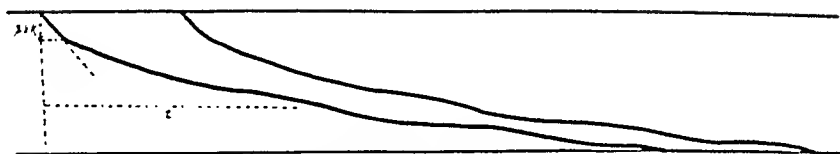


Abb. No. 4. Ausatemungskurve der VK bei einem schweren Emphysem. M. R., 57 J., 156 cm, 45 kg, emphysema pulm. $I_{VK} = -4.0$.

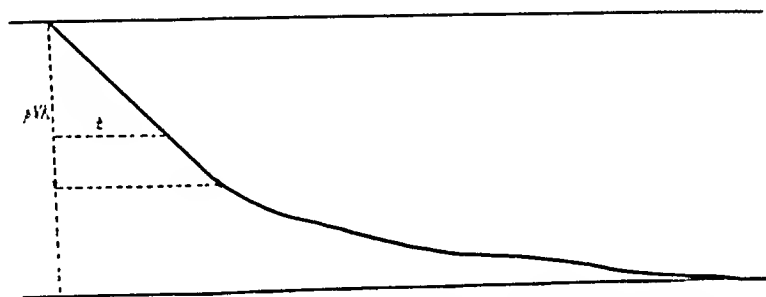


Abb. No. 5. Ausatemungskurve der VK bronchitischen Charakters. M. F., 50 J., 165 cm, 62 kg, bronchitis chron. $I_{VK} = +0.8$.

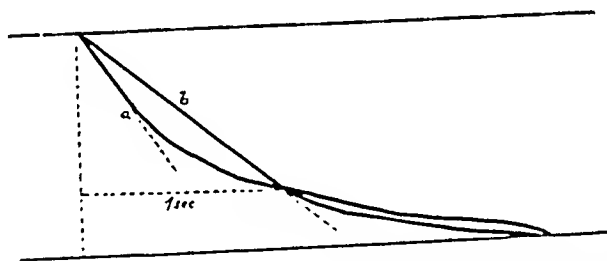


Abb. No. 6. I_{VK} der Kurve $a = 0.0$; I_{VK} der Kurve $b = +0.1$. Erklärung siehe im Text.

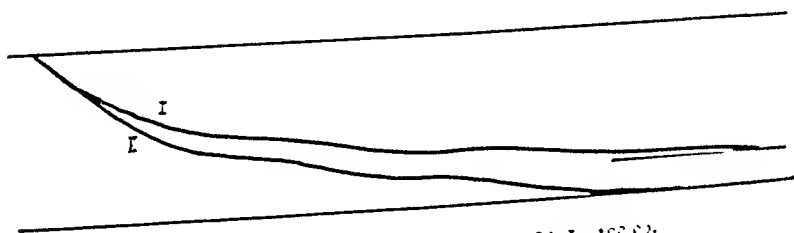


Abb. No. 7. W. F., Stenosis valv. mitr., fibrillatio atriorum. 51 J., 168 cm;
I. 3.1.1951. Dekompensiert, Leberstauung, Oedeme der unteren Extremitäten. $I_{VK} = -3.4$.
II. 10.1.1951. Nach Digitalisierung, Oedeme verschwunden, Leber zurückgefallen.
 $I_{VK} = -0.5$
VK bei beiden Untersuchungen bleibt beinahe gleich.



Abb. No. 8. J. M., stenosis valv. mitr., fibrillatio atriorum. 46 J., 162/87.
 I. 15.3.1951. Mit Digitalis überdosiert, schwere Lungenstauung, $I_{VK} = -1.5$.
 II. 19.3.1951. Nach Bettruhe, Koffein, Cardiophyllin. $I_{VK} = -0.9$.
 VK bei beiden Untersuchungen gleich.



Abb. No. 9. J. Š., ins. valv. mitr., 21 J., 169/59.
 I. 18.11.1950. Ascites, Oedeme der unteren Extremitäten, $I_{VK} = -2.7$.
 II. 13.12.1950. Nach Strophanthin und Digitalis Kur kompensiert. $I_{VK} = +0.25$.

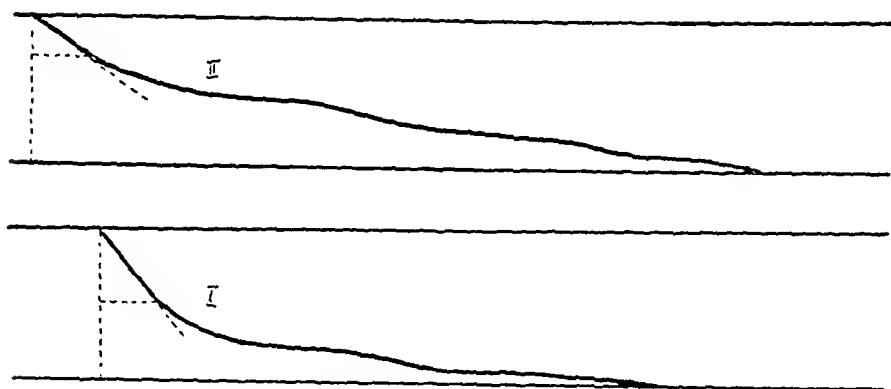


Abb. No. 10. I. S. F., myodegeneratio cordis decomp. 69 J., 167/84. $I_{VK} = -0.9$.
 II. K. F., cor pulmonale decomp. 54 J., 160/56. $I_{VK} = -3.7$.
 In beiden verglichenen Fällen ist die VK gleich gross, die Kurve No. II weist aber einen niedrigeren I_{VK} aus, es handelt sich hier um ein begleitendes Emphysem.

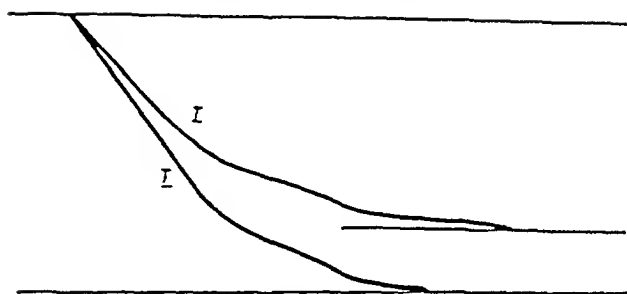


Abb. No. 11. V. Š. asthma bronchiale, 53 J., 153/45.

I. Atmungsbeschwerden, ohne Anfall, vor Inhalation $\text{IvK} = + 0.2$.

II. Nach einer Inhalation von 2 cem Bronchhydrin, ohne Beschwerden. $\text{IvK} = + 2.2$.

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The Hyperophthalmopathic Type of Graves' Disease.

19 cases treated with pituitary and orbital roentgen irradiation.

By

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(Submitted for publication November 2, 1953.)

The clinical picture of Graves' disease is capable of wide variation. This was realized as long ago as 1782 by Parry and stressed by Graves in 1835. Thus, the ocular disturbances may be slight or absent in one case and prominent in another. One of the first to describe a case of Graves' disease with exophthalmos (with corneal destruction) severe enough to require bilateral enucleation was Lorenz (1857). Associated exophthalmos with corneal destruction was also reported in a case described by von Basedow (1840). Dobyns (1950), who perused all relevant literature available, traced 95 cases of Graves' disease with severe ocular changes, including corneal ulceration.

On the basis of a life-long study of the clinical manifestations of Graves' disease Means (1945) recognised three types of the affection:

1. thyrotoxicosis without ophthalmopathy,
2. thyrotoxicosis with ophthalmopathy (classic type of Graves' disease),
3. hyperophthalmopathic type with hyper-, eu- or hypo-thyroid function.

Ocular Changes.

The clinical picture of the classical form of Graves' disease includes eye changes, which produce no symptoms. On the other hand, in the hyperophthalmopathic form the ocular disturbances most often are dominant and more or less troublesome.

The ocular manifestations occurring in these two forms of the disease are summarized in Table 1. (Partly according to Means).

The widened rima in the classical form of Graves' disease conveys the impression of true exophthalmos, *i. e.* protrusion of the bulb. Such protrusion is, however, only

Table 1.
Eye signs in Graves' disease.

Eye signs associated with classic type of Graves' disease.	Eye signs associated with hyperophthalmopathic type of Graves' disease.
Stare and tension of musculature around eyes.	True forward displacement of eye balls.
Lid retraction. Lid lag. Globe lag.	Gritty sensation in eyes. Lacrymation. Photophobia. Chemosis.
Lids often less bulging, show characteristic folds, which are exaggerated by weight loss.	Bulging of the lids especially at points where retrobulbar tissue protrudes around globe.
Soft cushion effect when pressure applied to globes. Orbital tension not abnormally increased.	Resistance when pressure applied to eye—globe backward. Orbital tension often increased.
Little if any extra-ocular weakness; no diplopia.	Often extra-ocular muscle weakness or paralysis; frequently diplopia.

apparent and is due to increased tone of the sympathetic-innervated smooth musculature of the eyelids. This increase in tone is explained by the increased amount of circulating thyroid hormone and consequent adrenalin-sensitization of such smooth muscle. The presence of such sensitization is readily demonstrated by Loewi's test.

Pathology.

In the hyperophthalmopathic type of the disease the patient has true exophthalmos due to retrobulbar changes and not, as formerly believed, to increased tone of the sympathetic-innervated smooth circular fibers (Müller's muscle) and of the smooth muscle of the fascia bulbi. The morbid anatomy of the orbits has been described by many workers in this field (Foster Moore 1920, Naffziger 1931 and 1933, Smelser 1937 and Mulvany 1943).

It is now generally agreed that the initial changes consist of increased retrobulbar pressure due to oedema of the retrobulbar fat, of the connective tissue and of the extrinsic muscles of the eye, and infiltration of round cells, especially lymphocytes, round the vessels. The histologic picture resembles that of chronic inflammation. The oedema and cellular infiltration are sometimes so severe as to cause stasis of the eyeballs, conjunctivitis, keratitis and papilloedema ending in panophthalmitis. If the retrobulbar process is less fulminant, gradual organization and cicatrization may occur at the site of the retrobulbar changes. This implies that the longer the exophthalmos remains untreated the greater the risk of irreparable injury due to scar formation. On the other hand, cumulative evidence suggests that the hyperophthalmopathic type of the disease can heal spontaneously with complete or partial disappearance of the ocular disturbances. *It is, however, not possible to predict the course of the eye changes.*

Aetiology.

The existence of a functional relationship between the anterior lobe of the pituitary and the thyroid gland has long been known. Removal of the pituitary of experimental animals is followed by atrophy of the thyroid, while extirpation of the thyroid causes hypertrophy of the anterior lobe of the pituitary. Feeding with thyroid extract — even in large doses — has never been known to produce true exophthalmos in animals or in man. In 1930 Loeb & Bassett showed in guinea-pigs that injections of anterior hypophyseal extract is capable of stimulating the thyroid, which becomes large and hyperactive. The first to produce exophthalmos in animals by the injection of anterior hypophyseal extract was Schockaert (1932). Soon afterwards Loeb & Friedmann (1932) showed that the administration of this extract to experimental animals is also capable of causing hyperplasia of the thyroid, hyperthyroidism and exophthalmos.

In 1932 Marine & Rosen reported that exophthalmos can be produced quicker in thyroidectomized animals. Whether hyperplasia of the thyroid and exophthalmos are caused by one and the same agent, namely the thyrotrophic hormone of the anterior pituitary, or by two chemically similar principles, is a point on which no general agreement has been reached (Friedgood, 1941). In 1937 Smelser pointed out the striking similarity between the orbital changes in experimental and clinical exophthalmos. In both cases orbital oedema is prominent. Paulson (1937) reported an appreciable increase in the water content of the orbital tissue in experimental exophthalmos. A reasonable explanation of this increase in interstitial fluid has been offered by Ludwig, Boas & Soffer (1950) and by Asboe-Hansen & Kurt Iversen (1951). Using special histochemical methods they demonstrated an accumulation of mucopolysaccharides, especially hyaluronic acid, in the orbital tissue of animals with experimental exophthalmos. As this substance is capable of binding large amounts of water, its presence can explain the swelling of the loose orbital tissue. It appears that orbital tissue from human beings with the hyperophthalmopathic type of Graves' disease has not been studied for such substances. However, an accumulation of hyaluronidase-sensitive, acid mucopolysaccharide has been demonstrated in the skeletal muscle of patients with this type of disease (Asboe-Hansen & Kurt Iversen, 1951).

Increased urinary excretion of thyrotrophic hormone by patients with the type of disease under discussion has often been reported.

In 1944 De Robertis & Del Conte described a method for determining the amount of thyrotrophic hormone in the blood. They found the blood level of the thyroid stimulating hormone (TSH) to be elevated in the presence of the hyperophthalmopathic type of Graves' disease (4 cases), but depressed in the classical type (4 cases). In 1949 D'Angelo & Gordon using tadpoles devised a method for determining both the TSH and the thyroid hormone in the blood and confirmed the findings made by De Robertis & Del Conte. Robert Wichmann (1952), who used a modification of the lastmentioned method, studied the level of the TSH in the blood. He found it to be elevated in the hyperophthalmopathic type (11 out of 12 cases) but not in the classical type (5 cases).

Observations made at neurosurgical operations strongly suggest that hypophyseal changes play a prominent causative rôle in the ocular disturbances seen in association with the hyperophthalmopathic type of Graves' disease. Gardner (1937) was the first to report a beneficial effect of division of the hypophyseal stalk and destruction of the anterior lobe of the pituitary with electrocoagulation. When reviewed 7 years later the patient was still free from eye symptoms. Rasmussen & Gardner (1940) reported excellent results in another case that they had followed up for 5 years. McCullagh (1946) reported 2 cases treated with unilateral craniotomy and electrocoagulation of the anterior lobe of the pituitary. In these 2 cases treatment had the desired effect on *both* eyes, but the improvement was attended by signs of hypophyseal insufficiency. In one of the patients the insufficiency was severe with associated testicular atrophy, impotence, decreased urinary gonadotrophin and 17-ketosteroids as well as signs of hypoglycaemia.

Evidence available thus suggests that increased production of thyrotrophic hormone is capable of causing the hyperophthalmopathic type of Graves' disease.

Most cases of progressive exophthalmos have appeared after thyroidectomy. A probable explanation of this was offered by Rawson (1948), who showed that the thyrotrophic hormone is inactivated by thyroid tissue. Inactivation was greatest with thyroid tissue changed by diffuse thyrotoxicosis. This suggests the conclusion that *in all cases in which thyrotoxicosis is of central origin (hypophysis, hypothalamus), an active attack on the thyroid involves the risk of progressive exophthalmos.* This applies not only to thyroidectomy, but also to thionurcil therapy and treatment with radioactive iodine compounds. Ample evidence is available of the occurrence of progressive exophthalmos following such therapeutic measures.

Several voices have been raised against the assumption that the hyperophthalmopathic type of Graves' disease is due to overproduction of the thyrotrophic hormone, it being objected that if this were so, it would be difficult to explain the rarity of progressive exophthalmos in patients with myxoedema. If it were possible to trace the primary cause of this disease to the thyroid with certainty, this objection would be justified, because then decreased thyroid activity would imply an increased production of thyrotrophic hormone. But in most cases of spontaneous myxoedema it is not possible to trace the site of the primary causal factor. If the disease were of hypophyseal or hypothalamic origin, one might expect decreased production of thyrotrophic hormone and consequently no ocular disturbances. With this in mind De Robertis (1948) studied the level of the thyrotrophic hormone in the blood of patients with myxoedema and noted that it was elevated in some but depressed in others. A case of spontaneous myxoedema with ocular disturbances of the type under consideration (Case No. 19, Tables 3 and 4) is described in a later section.

General Remarks and Material.

In a case of Graves' disease with extremely malignant exophthalmos threatening vision, roentgen therapy produced an excellent result. It was this favourable re-

sponse of the condition that prompted us to focus our attention on the ocular symptoms of the disease under consideration.

The present series consists of 19 cases of the hyperophthalmopathic type of Graves' disease treated some time between April 1950 and August 1952.

The differential diagnosis was based mainly on the ocular manifestations. In this connection it might be useful to point out that the ocular phenomena of the classical type of thyrotoxicosis usually are readily distinguished from those of the hyperophthalmopathic type (Table 1). All of the patients were submitted to

Table 2.
Age- and Sex-distribution.

Age in years	Number of men	Number of women	All cases
20-30	1	1	2
31-40	1	3	4
41-50	1	3	4
51-60	3	3	6
61-70	1	2	3
Total	7	12	19

ophthalmologic examination including measurement of the degree of any exophthalmos by means of Hertel's exophthalmometer. The normal range of variation of these values is wide. Thus Knudtzon (1949), who studied a large series of healthy persons, found the values to vary between 11 mm and 24 mm in men and between 12 mm and 22 mm in women with an overall average of about 17 mm. Knudtzon also suggested that values of more than 22 mm should be considered pathologic. This does not, however, exclude the possibility of exophthalmos before such a critical level is reached: therefore a single determination is not always conclusive. From 1951 onwards we also used an orbitometer of the type described by Cooper (1948). With this apparatus it is possible to measure both the degree of exophthalmos and the retrobulbar pressure. In his series of the classical type of Graves' disease Cooper found that the orbital tension was not increased. In his series of the hyperophthalmopathic type of Graves' disease, however, retrobulbar tension was usually increased. This in combination with the other ocular disturbances in these patients is also a useful sign for differentiation from the classical type. It should, however, be mentioned that in some of our cases the retrobulbar tension was normal despite a clear-cut clinical picture of the hyperophthalmopathic type. It may probably be assumed that retrobulbar pressure is not increased until the bulb can no longer be extruded, after which increased pressure may cause venous stasis with the risk of subsequent malignant exophthalmos.

In the present series no determination were made of the level of the thyrotrophic hormone in the blood or in the urine. (A simple procedure for routine clinical determination of the thyrotrophic hormone in the blood or urine is still badly needed.)

More than half of our patients (11 out of 19) had earlier been submitted to thyroidectomy because of hyperthyroidism. Of these 11 patients, 6 had exophthalmos.

before the operation. After operation the symptoms progressed in 5 of them and persisted unchanged in the sixth. In the remaining 5 patients eye symptoms had not appeared until after thyroidectomy. This suggests that all of the patients operated on had the hyperophthalmopathic type of the disease from the beginning.

Of the 11 thyroidectomized patients, 5 showed signs of persisting thyrotoxicosis and 3 of hypothyroidism. In the remaining 3 thyroid function was apparently normal. Of the 8 non-operated cases hyperthyroidism was observed in 5, hypothyroidism in 1 and euthyroidism in 2.

Treatment.

All of the patients received radiotherapy. The 4 patients who had hypothyroidism before irradiation also received desiccated thyroid. In theory this treatment may suppress pituitary function and may be useful in the management of mild cases, but Dobyns (1950), Jones (1951) and others have reported excessive deterioration of the eyes despite medication with large doses of desiccated thyroid.

In 10 cases the roentgen rays were applied to the pituitary region, in 6 to the pituitary region and afterwards to the orbits, and in 3 cases to the orbits only.

Technique.

The *hypophysis* was as a rule irradiated via 4 temporal fields, measuring 5 cm \times 6 cm each. F S D: 50 or 60 cm. Filtration: 0.5 mm Cu and 1 mm Al; 170 kv, 15 ma. H V L: 0.9 mm Cu. One field per day was irradiated with a dose of 300 r. Treatment was as a rule given in the form of 2 series at an interval of about 5 weeks. In the first series each field received altogether 1,500 r, in the second series 600–900 r. The dose applied to the hypophyseal region was calculated as 30–35 per cent of the skin dose per field. With this technique it is not only the hypophysis that is irradiated but also the posterior region of the orbits. Regarding the distribution of the dose among different parts of the orbits, reference is made to an experimental study described elsewhere.¹

In irradiation of the *orbits* the rays were directed against those parts of the orbit located behind the lens. The size of the field ranged from 10 cm² to 20 cm². F S D: 50 cm. Filtration: 0.5 mm Cu and 1 mm Al; 170 kv, 15 ma. H V L: 0.9 mm Cu. The orbits were treated with a daily skin dose of 100–150 r. As a rule treatment was given in 2 stages at an interval of 4–5 weeks. In the first series the total skin dose was 900 r per field. The dose applied to the middle of the posterior of the orbit was calculated as 60–70 per cent of the skin dose.

Frontal irradiation of the orbits was avoided owing to the risk of cataract (Poppe, 1912).

The results of roentgen therapy are summarized in tables 3–7.

¹ To be published in *Acta radiologica*.

Table 3.

Röntgen treatment of the hypophysis and posterior part of the orbits.

Effect on eye symptoms.

Case No. Journal No.	Sex	Age	Lacrymation	Photophobia	Ophthalmoplegia	Eye lid oedema	Chemosis	Hertel values mm		Orbitometry	Calculated focal dose ¹ in region of hypophysis r/nr. of days	Follow-up in months
								Right	Left			
3; 2432 50	M	52									2,200 r/22 d. 3,600 r/83 d.	33
Before roentgen ...			—	—	+	+	—	26	26	—		
After roentgen ...			—	—	—	—	—	23	23	normal		
4; 3029/50	F	62									2,100 r/23 d. 3,000 r/73 d.	31
Before roentgen ...			—	—	+	—	—	18	17.5	—		
After roentgen ...			—	—	—	—	—	16	16	normal		
6; 3760 50	F	39									2,200 r/27 d. 3,100 r/81 d.	28
Before roentgen ...			—	—	—	+	—	17	17	—		
After roentgen ...			—	—	—	—	—	15	15	normal		
7; 697 50	F	55									2,000 r/25 d. 2,800 r/83 d.	28
Before roentgen ...			+	—	—	+	—	20	21	normal		
After roentgen ...			—	—	—	—	—	20	21	normal		
10; 540 51	F	39									2,200 r/23 d. 3,100 r/68 d.	26
Before roentgen ...			—	—	—	—	—	21	21	—		
After roentgen ...			—	—	—	—	—	18	19	normal		
15; 2303 51	M	64									2,000 r/23 d. 3,200 r/69 d.	21
Before roentgen ...			+	+	—	—	+	22	21	pathologic		
After roentgen ...			—	—	—	—	—	13	15	normal		
16; 2817 51	F	42									2,200 r/18 d. 3,000 r/60 d.	19
Before roentgen ...			+	+	+	+	+	23	20	pathologic		
After roentgen ...			—	—	—	Less	—	20	18	pathologic		
17; 3416 51	F	23									2,200 r/28 d. 3,100 r/72 d.	18
Before roentgen ...			+	—	—	+	—	21	21	normal		
After roentgen ...			—	—	—	—	—	21	21	normal		
18; 492 52	F	32									3,100 r/68 d. 4,400 r/118 d.	14
Before roentgen ...			+	—	—	+	—	17	16	normal		
After roentgen ...			—	—	—	—	—	17	17	normal		
19; 817 52	F	48									2,900 r/22 d.	10
Before roentgen ...			+	—	—	+	—	23	23	normal		
After roentgen ...			—	—	—	—	—	21	21	normal decreased		

Patients Nos. 7, 10, 16 and 18 had undergone thyroidectomy.

¹ The figures indicate the total focal dose after each series of roentgen treatment. In the posterior of the orbits the total focal dose is about 8 per cent larger.**Comments on the Results of Roentgen Therapy.***Irradiation of the Hypophysis and Posterior Part of the Orbits.*

In 10 cases of the hyperophthalmopathic type of Graves' disease this therapy produced the following effect on the ocular disturbances. All troublesome eye symptoms disappeared. Among the 7 cases with oedema of the eyelids, the swelling

Table 4.

Roentgen treatment of the hypophysis and posterior part of the pituitary gland.
Effect on thyroid function.

Case No.	Weight in kg	Pulse	Blood pressure	BMR %	Iodine test, ¹ Values indicate percentage in thyroid after 24 hours.	Serum cholesterol mg (0.1 ml)	General symptoms
3 Before	73	100	120/80	+ 22	—	169	Loss of weight
After	79	75	150/80	+ 19	52	153	None
4 Before ...	75	80	210/120	+ 17	—	196	Increased irritability
After	81	80	250/130	— 8	40	259	None
6 Before ...	62	80	125/60	+ 21	—	125	Palpitations, loss of weight, increased ir- ritability
After	70	65	125/85	— 10	28	211	None
7 Before ...	66	—	—	+ 3	—	—	Increased irritability
After	61	80	170/95	± 0	58	229	None
10 Before ...	72	95	160/100	+ 21	—	195	Palpitations, pers- piring, tremor
After ...	76	90	160/100	—	36	398	None
15 Before ...	74	80	150/80	+ 75	77	209	Palpitations, loss of weight, increased ir- ritability, perspiring
After	90	60	160/95	— 45	21	577	None
16 Before ...	61	100	145/90	+ 26	—	233	None
After	64	85	110/70	— 4	37	233	None
17 Before ...	55	90	135/80	+ 15	67	232	Palpitations, loss of weight, increased ir- ritability, perspiring
After	57	76	135/80	— 5	39	204	None
18 Before ...	59	90	140/60	+ 11	41	148	Cardiac arrhythmia
After	62	80	160/55	+ 10	37	192	None
19 Before ...	66	80	130/80	— 25	6	205	Myxedema
After	64	80	130/75	+ 7	8	241	Symptom free after thyroid.

Patients Nos. 7, 10, 16 and 18 had undergone thyroidectomy.

¹ The iodine test was not used until Jan. 1952.

disappeared in 6 and decreased in 1. Chemosis, which was present in 2 of the patients, disappeared. In 7 cases the Hertel values diminished by 2 to 9 mm; no such change was recorded in the other 3. In 4 cases the patients were not studied orbitonometrically before roentgen treatment, because the apparatus was not available at that time. In 4 cases orbitonometry recordings lay within a normal range despite prominent ocular changes. In the remaining 2 the retrobulbar tension was increased before roentgen treatment. In one of them the pressure returned to normal. In the other the increased pressure persisted unchanged despite the disappearance of

Table 5.

Röntgen treatment of the hypophysis and posterior part of the orbits and subsequent irradiation of the anterior part of the orbits.

Effect on eye symptoms.

Case No. Journal No.	Sex	Age	Lacrymation	Photophobia	Ophthalmoplegia	Eye lid oedema	Chemosis	Hertel values mm		Orbi- tono- metry	Calculated focal dose ¹ in		Followup in months
								Right	Left		region of hypophysis r./nr. of days ²	anterior part of orbit r./nr. of days	
2; 1662/50	M	59									2,200 r/21 d. 4,000 r/76 d.	800 r/11 d. 1,400 r/58 d.	35
Before roentgen (hypophysis)			—	—	+	+	—	14	17	—			
Before roentgen (orbits)			—	—	+	+	—	14	17	—			
After roentgen			—	—	—	—	—	14	17	normal			
5; 1016/48	F	50									1,700 r/12 d. 2,900 r/75 d. 4,000 r/169d.	700 r/8 d. 1,100 r/75 d.	28
Before roentgen (hypophysis)			—	—	—	+	—	26	26	—			
Before roentgen (orbits)			—	—	—	+	—	26	26	—			
After roentgen			—	—	—	+	—	26	26	normal			
8; 3775/50	M	35									2,200 r/22 d. 3,100 r/66 d. 4,600 r/169d.	700 r/7 d.	28
Before roentgen (hypophysis)			+	+	+	+	—	32	30	—			
Before roentgen (orbits)			+	+	—	+	—	29	29	—			
After roentgen			—	—	—	—	—	24	24	normal			
9; 113/51	M	48									2,000 r/24 d. 2,900 r/80 d. 4,200 r/162d.	700 r/15 d. 1,300 r/71 d.	28
Before roentgen (hypophysis)			+	—	+	+	+	27	28	normal			
Before roentgen (orbits)			+	—	+	+	+	27	28	normal			
After roentgen			—	—	+	—	—	27	28	normal			
12; 1407/51	F	70									2,200 r/22 d. 3,500 r/89 d.	800 r/10 d.	23
Before roentgen (hypophysis)			+	—	—	+	—	21	23	normal			
Before roentgen (orbits)			—	—	—	+	—	21	23	normal			
After roentgen			—	—	—	—	—	21	23	normal			
14; 2017/51	F	54									2,200 r/22 d. 3,000 r/73 d.	400 r/4 d.	21
Before roentgen (hypophysis)			+	—	+	+	—	24	24	normal			
Before roentgen (orbits)			+	—	+	+	—	24	24	normal			
After roentgen			—	—	—	—	—	22	22	normal			

Patients Nos. 5, 8, 9 and 12 had undergone thyroidectomy.

¹ The figures indicate the total focal dose after each series of roentgen treatment.

² In the posterior of the orbits the total focal dose is about 8 per cent larger.

lacrymation, photophobia, ophthalmalgia and chemosis and decrease in the oedema of the eyelids and of the exophthalmos. In one case the originally normal orbital tension decreased in association with the disappearance of the other ocular manifestations following irradiation. Thus, *roentgen therapy produced a definitely beneficial effect on the eye symptoms in all of these 10 cases.*

Table 6.

Röntgen treatment of the hypophysis and posterior part of the orbits and subsequent treatment of the anterior part of the orbits.

Effect on thyroid function.

Case No.	Weight in kg	Pulse	Blood pressure	BMR %	Iodine test: Values indicate percentage in thyroid after 24 hours	Serum cholesterol mg/100 ml	General symptoms
2 Before ...	82	72	125/75	+ 4	—	150	Palpitations, profuse sweating, tremor
After	83	65	115/65	- 16	16	245	None
5 Before ...	68	70	135/70	- 3	—	180	Increased irritability
After	51	80	110/65	+ 6	—	210	As before
8 Before ...	69	80	140/90	+ 6	—	122	None
After	74	72	140/90	- 11	33	228	None
9 Before ...	90	—	—	- 10	—	185	None
After	90	70	140/80	- 1	11	185	None
12 Before ...	—	—	220/110	+ 20	—	216	Profuse sweating, increased irritability
After	65	80	225/105	+ 5	45	208	None
14 Before ...	64	75	130/80	+ 16	—	153	None
After	67	70	120/80	+ 3	31	205	None

Patients Nos. 5, 8, 9 and 12 had undergone thyroidectomy.

* The iodine test was not used until Jan. 1952.

Table 7.

Röntgen therapy of the orbits only.

Effect on eye symptoms.

Case No.	Sex	Age	Lacrimation	Photophobia	Ophthalmoplegia	Eyelid oedema	Chemosis	Proptosis	Visual acuity	Defect of visual field	Hertel values mm	Orbitalometry	Calculated focal dose rads, of days	Relief of symptoms
Journal No.									Right	Left	Right	Left		
1; 1128/50	M	57											700 r d. 1,000 r 14 d.	30
Before			+	+	+	+	+	+	0.3	2/60	+	22	21	normal
After			—	—	—	—	—	—	1.0	0.1	—	20	20	
11; 3227/47	F	51											700 r d. 1,500 r 7 d.	20
Before			—	—	—	+	—	—	1.0	1.0	—	21	21	path. high
After			—	—	—	+	—	—	1.0	1.0	—	21	21	path. high
13; 1838/51	M	28											200 r 7 d.	20
Before			+	—	—	+	—	—	1.0	1.0	—	21	21	normal
After			—	—	—	—	—	—	1.0	1.0	—	21	21	

All patients had undergone thyroidectomy.

* Figures indicate the total focal dose after each series of treatment.

Of the 10 patients with the hyperophthalmopathic type of Graves' disease treated with the above-described type of irradiation, 8 had already hyperthyroidism before irradiation (Table 4). In 4 of them thyroid activity returned to normal level. Two became symptom-free, the only clinical sign of thyrotoxicosis then being a slightly pathologic I^{131} test. In 2 cases the basal metabolic rate decreased and the blood cholesterol was increased, but neither of the patients had symptoms of myxoedema. They were afterwards treated with desiccated thyroid. Euthyroidism in 1 of the patients was unaffected by roentgen therapy. In the remaining case, in which the patient had hypothyroidism, this disease had been treated with desiccated thyroid from the beginning.

Thus, *roentgen treatment of the pituitary region depressed thyroid function in all of these 8 patients who originally had hyperthyroidism.*

In case 15 (Tables 3 and 4, figures I and II) irradiation of the pituitary and posterior of the orbits produced a striking effect:

A male, aged 64, was admitted on Aug. 11, 1951 (MJ 1902/51 and RJ 2303/51) because of the hyperophthalmopathic type of Graves' disease with hyperthyroidism.

History. — The patient gave an 11 months' history of increased irritability, profuse sweating, palpitation, tremor, increasing ocular proptosis, increased lacrymation and shortness of breath.

On admission. — Diffuse enlargement of the thyroid gland, tremor of the tongue and fingers. Pulse rate 80/min. Blood pressure: 150/80. The basal metabolic rate, as measured on various occasions, was about plus 75 per cent. Serum cholesterol: 200 mg/100 ml. Body-weight 74 kg. Roentgen examination of the heart and electrocardiographic studies showed no signs of a pathologic condition. Auricular fibrillation appeared while the patient was in hospital. Normal visual acuity. The field of vision and the intra-ocular pressure were normal. Fundus oculi were of normal appearance. Degree of exophthalmos (Hertel): right eye 22 mm, left 21 mm. Orbitonometric examination showed distinctly increased retrobulbar pressure on both sides. Application of a pressure of 400 gm to each eye produced a backward displacement of only 4 mm (with these Hertel values this pressure should produce a displacement of at least 7 mm). The orbitonometric curves were flat. Acute right conjunctivitis with corneal ulceration appeared while the patient was in hospital. This complication was accompanied by a slight swelling of both eyelids and slight conjunctivitis of the left eye.

Treatment. — Roentgen treatment of the hypophysis and posterior region of the orbits was started without delay. The calculated dose in the region of the pituitary was 2,000 r/23 days. After 5 weeks' interval a second series was given. The total dose delivered to the pituitary and the posterior of the orbit was thus 3,200 r/69 days.

Follow-up. — The patient was reviewed several times during and after treatment. Gradual improvement was noted, but even three and a half months after treatment the auricular fibrillation persisted and the basic metabolic rate was about plus 40 per cent. The iodine test showed a pronounced accumulation (77 per cent) of the test dose after 24 hours. He had, however, gained 9 kg, the ocular changes no longer troubled him and the eye symptoms had completely subsided. The cornea had healed. Visual acuity and field of vision were normal. The exophthalmos (Hertel values) had decreased by 4 mm. on the right side and by 2 mm on the left. Orbitonometry showed considerable diminution of the increased retrobulbar pressure on both sides.

One year after treatment the patient still had no eye symptoms. Normal sinus rhythm. He had increased 20 kg in body-weight. The iodine test now showed normal values. The basic metabolic rate was minus 17 per cent. Blood pressure 165/95. Blood cholesterol



Fig. 1. Case No. 15 (tables 3 and 4) before treatment. No obvious exophthalmos in spite of \pm increased retrobulbar pressure on both sides. Slight oedema of the lids, conjunctivitis and \pm corneal ulceration on the right side.



Fig. 11. The same patient 1 year and 3 months after the beginning of treatment (external irradiation of the hypophysis and posterior of the orbits). No eye symptoms and \pm normal retrobulbar pressure on both sides.

370 mg./100 ml. Ophthalmologic examination revealed no signs of a pathologic condition. Exophthalmos (Hertel values) had decreased to 13 mm on the right side (total decrease 9 mm) and to 15 mm on the left side (total decrease 6 mm). Orbitonometric recordings now lay within a normal range.

Recive 15 months after treatment. — Eyes: as before, same degree of exophthalmos (Hertel values), normal retrobulbar pressure on either side. The thyroid was not enlarged. The basic metabolic rate had, however, decreased to minus 45 per cent, and the cholesterol had increased to as much as 577 mg/100 ml. No further change in body-weight was noted. He was symptom-free and showed no other signs of hypothyroid function. Working capacity (mechanic) had not diminished. The patient received a moderate dose of desiccated thyroid. The tests performed suggested no impairment of the other functions of the pituitary.

Same Treatment as Before plus Roentgen Irradiation of the Anterior Parts of the Orbits.

In 6 cases the patient initially received similar roentgen treatment of the pituitary and posterior part of the orbits, but as the effect on the ocular changes was unsatisfactory, the anterior part of the orbits was also irradiated.

The results achieved by this combined treatment may be summarised as follows. The eye symptoms originally present in 5 of the 6 cases, disappeared in 4. In all 6 cases the patients had eyelid oedema, which the roentgen treatment controlled completely in 5. Chemosis, which was present in 2 cases, disappeared. Exophthalmos (Hertel values) decreased by 2 mm and 8 mm in 2 cases: in the remaining 4 it remained unchanged, despite the disappearance of all other eye symptoms in 3 of them. In no instance did the ocular changes progress during the observation period. Despite high initial Hertel values orbitonometric measurements were normal in 3 cases both before and after roentgen therapy. In the other 3 cases orbital tension was not measured before irradiation.

Of the 6 patients with the hyperophthalmopathic type of Graves' disease treated with roentgen of both the pituitary and the orbits, 2 originally had hyperthyroidism (Table 6): in one of them treatment depressed thyroid function to normal. In the other case the patient now had laboratory signs of hypothyroidism, but he was otherwise symptom-free.

In 3 cases thyroid activity was normal both before and after roentgen treatment. One patient had hypothyroidism from the beginning and received desiccated thyroid.

Case 9. — In this case (Tables 5 and 6) irradiation of the hypophysis and orbits did not produce such a striking effect. A man, aged 50; who was admitted on Dec. 12, 1950, because of progressive exophthalmos following thyroidectomy.

History. — Signs of increasing thyrotoxicosis during the last 11 months. Before thyroidectomy — 7 months before admission — the basal metabolic rate was about + 50 per cent. At that time there were no signs of exophthalmos. Pathologic-anatomical diagnosis: toxic goiter treated with iodine. The primary effect of operation was good. However, 5 months later, i. e. 2 months before admission, both eyes began to protrude, the eyelids began to swell, and intra-ocular pressure and lacrymation increased.

On admission. — The patient was in a good general condition. The thyroid was palpable. Pronounced bilateral proptosis, swelling of eyelids and slight chemosis were noted.



Fig. III. Case No. 8 (Tables 5 and 6) before treatment.



Fig. IV. The same patient 2 years and 3 months after the beginning of treatment, all with irradiation of the pituitary region followed by the same treatment of the pituitary.

Alternating divergent squint of 10° was observed. The range of mobility of the eyeballs was not limited, there was no diplopia, and the ocular fundi, field of vision, visual acuity and intra-ocular pressure were normal. Hertel: right 27 mm, left 28 mm. The basal metabolic rate, as measured on several occasions, was — 10 per cent. Blood cholesterol 185 mg/100 ml.

Treatment. — The patient was medicated with desiccated thyroid for 3 weeks with an initial daily dose of 0.4 mg. which was soon increased to 1.2 mg. Despite this medication, the eye symptoms, diplopia, and increased lacrymation, progressed. Ophthalmological examination: Hertel values as before, but the divergent squint had increased from 10° to 20°. The diplopia chart showed limited mobility of the left bulb. No definite signs of paresis of the outer muscles of the eye were demonstrable. Bilateral conjunctivitis was observed.

As signs of progressive exophthalmos had been present for almost 3 months, irradiation of the hypophysis and of the posterior part of the orbits was started. The patient received 3 series of roentgen treatment directed to these regions and 2 series of such treatment against the anterior of the orbits. Medication with desiccated thyroid (0.4 mg per day) was continued. The total dose delivered to the hypophysis and the posterior part of the orbits was 4,200 r/162 days. The focal dose delivered to the anterior part of the orbits was 1,300 r/71 days.

Follow-up. — At review 2 months after the commencement of treatment the lacrymation was no longer increased. Diplopia was as before. The eyelids were less puffy. Hertel values, visual acuity, ocular fundi and field of vision as before.

Fifteen months after the end of treatment the patient showed no further changes in the condition of the eyes. The process had evidently burnt itself out and left behind fibrous changes, irresponsive to irradiation. The basal metabolic rate was — 1 per cent with the same dose of desiccated thyroid as before. The blood cholesterol was 185 mg/100 ml. Body weight was unchanged and the other hypophyseal functions were apparently normal.

Roentgen Treatment of the Orbits.

In cases 1, 11 and 13 the patients received roentgen treatment of the orbits only (Tab. 7). In cases 1 and 13 thyroidectomy had been followed by the appearance of hypothyroidism, for which the patients were treated with desiccated thyroid before, during and after irradiation.

In case 11, the patient, a woman aged 51, had been thyroidectomised many years earlier and had since received different kinds of treatment because of persistent thyrotoxicosis. Thyroid function was normal at the time of irradiation of the orbits. This patient, who had thus had exophthalmos for five years and a half, no longer had ocular trouble. Treatment was desired on purely cosmetic grounds. The retrobulbar pressure was increased on both sides. Orbital irradiation had no effect on the degree of exophthalmos (Hertel values) or on the increased retrobulbar pressure. The absence of ocular symptoms suggested that the disease was no longer active, an assumption supported by the absence of any response to irradiation. Behind the bulbs there was evidently fibrous tissue and not radio-sensitive oedema with round cell infiltration.

In case 13 of this group the response to irradiation was favourable. The ocular symptoms disappeared.

In case 1, a man aged 57, dramatic improvement was noted. Three years previously thyrotoxic symptoms, exophthalmos and diplopia appeared and, later, bilateral insufficiency of the extrinsic muscles of the eye. Two years after the onset of these symptoms he was submitted to subtotal thyroidectomy. Visual acuity was then: right 1.0, left 0.9. After operation the basal metabolic rate became normal, but the diplopia persisted.

Eight months after thyroidectomy exophthalmos recurred and progressed, and a few months later increasing impairment of vision was noted. Examination now revealed moderate exophthalmos, marked chemosis, oedema of the eyelids and diplopia. Visual acuity: right 0.3 and left 2/60. Bilateral papilloedema, temporal defect of the field of vision of the right eye and possibly defect of the left quadrant of the left eye for red and coloured objects were noted. The basal metabolic rate was minus 14 per cent. The patient had therefore received desiccated thyroid. Roentgenography of the orbits, sella turcica and encephalography showed no signs of a pathological condition. As the change indicated despite treatment with desiccated thyroid, the patient was offered orbital decompression, but refused.

We then began to irradiate the posterior portion of the orbits. The focal dose delivered to each orbit was 700 r/8 days. Daily control showed rapid improvement of visual acuity. Within 11 days visual acuity had increased from 0.3 to 1.0 on the left side and from 2/60 to 0.1 on the right. Protrusion of the eyeball had decreased by 1 mm bilaterally, chemosis had subsided and the defect in the field of vision showed regression. Four weeks later the patient received a second course of roentgen therapy, which brought the total focal dose delivered to each orbit up to 1,000 r. One year later the patient, a captain of the merchant marine, was symptom-free and able to return to work. When last seen, two and a half years after irradiation, visual acuity was 1.0 on the right side and 0.1 on the left. Field of vision: small para-central scotoma on the left side. The right side was normal. Ophthalmometric measurements were within a normal range.

General Comments on the Roentgen Treatment of the Hyperophthalmopathic Type of Graves' Disease.

A. Irradiation of the Pituitary.

Evidence is available that roentgen treatment of the pituitary can suppress increased hypophyseal function. Thus several investigators have reported a favourable effect of pituitary irradiation in the management of Cushing's disease and acromegaly. In these conditions cellular changes often occur in the anterior pituitary lobe: such changes are probably present also in the hyperophthalmopathic type of Graves' disease, but whether the primary causal factor is located in the hypophysis or more centrally (diencephalon) is unknown.

Observations made in the present series of the hyperophthalmopathic type of Graves' disease support the assumption that increased hypophyseal function can be partly or completely controlled by roentgen therapy. Thus in the 10 patients who originally had hyperthyroidism, this hyperactivity was controlled in all cases. Seven of the patients became clinically euthyroid. It is possible that the dose used sometimes produced an even stronger effect. Thus, judging by the basal metabolic rate and the blood cholesterol values in the other 3 cases, roentgen treatment had depressed the originally increased hypophyseal activity to subnormal level, but the patients showed no other clinical evidence of hypothyroid function.

In all of the cases with increased blood cholesterol values noted on various occasions after roentgen therapy, the patients were originally hyperthyroid. In 5 other cases the cholesterol values were higher than before irradiation but still lay within a normal range. Thus, of the 16 patients treated with roentgen of the pi-

pituitary, 3 afterwards showed persistent laboratory signs of hypothyroidism, but they were otherwise symptom-free. Investigation of the other functions of the pituitary by means of the adrenalin test, ACTH test, glucose and insulin tolerance tests, determination of the urinary 17-ketosteroids and 11-oxysteroids and urinary concentration test both during and at least 1 year after irradiation showed no signs of impaired hypophyseal function. Judging by the patients' reports, roentgen treatment had no effect on libido or ovarian function. Thus, pituitary irradiation had no demonstrable side effects on other functions of the pituitary. This in turn supports the view presented by others (Kaplan, 1911, Luft, 1946) that the dose necessary for controlling cellular hyperactivity is much smaller than that necessary to disturb the function of normal cells.

It therefore appears that this form of therapy can be used with advantage in the management of the hyperophthalmopathic type of Graves' disease. In our cases irradiation was extended to include the posterior region of the orbits. This probably partly accounts for the regression of the eye symptoms. However, the increased thyrotrophic activity of the anterior lobe of the pituitary must also have been diminished, because hyperactivity of the thyroid was controlled in all of the cases.

Good results of this form of treatment have been reported by Hertz, Means & Williams (1941), Borak (1935), Schwarz (1945), Beierwaltes (1951) and Hermann (1952). In 1950 Dobyns reported 37 published cases, of which 13 had improved, and he concludes that the method merits consideration. Friedgood, Russel Brain, Jones (1951) did not find roentgen therapy to have such a beneficial effect on the ocular disturbances.

Judging by the literature, some patients received fairly large total doses delivered to the pituitary without definite improvement, while others received a much smaller dose with good results. It seems justifiable to conclude that both the size and the distribution of the dose and the quality of the rays as well as the time factor and, above all, early treatment are important for securing good results. The total doses used in the present series are summarised in Tables 3 and 5.

B. Roentgen Treatment of the Ocular Orbits.

In our opinion orbital irradiation should preferably be given when the disease is in the acute stage with rapidly progressing, serious ocular changes. As pointed out above, the cellular infiltration and the oedema of the orbital and periorbital region appear to respond favourably to irradiation. But this treatment is, of course, only symptomatic and should be followed by irradiation of the hypophysis. In uncomplicated cases roentgen therapy should be directed mainly to the pituitary and posterior part of the orbits. If the eye symptoms do not respond satisfactorily, irradiation of the anterior part of the orbits is indicated. In cases of malignant exophthalmos Thomas & Woods, Ginsburg, Friedgood, Mandeville, Jones irradiated the orbits only. The results, although sometimes good, varied, probably with the amount of retrobulbar fibrous tissue. The focal doses employed in the present study are given in Tables 5 and 7.

Summary.

The pathology, pathogenesis, and clinical and differential diagnosis of Graves' disease are discussed and 19 cases treated with roentgen irradiation are described. In 10 cases roentgen treatment was given to the hypophysis and the posterior part of the orbits; in 6 of the other cases such treatment was followed by irradiation of the anterior part of the orbits. In the remaining 3 roentgen therapy was limited to the orbits only.

The observations made suggested that roentgen irradiation of the region of the hypophysis depresses any increased thyrotrophic activity of the anterior lobe of the pituitary, because hyperthyroidism always disappeared after such treatment. In the 16 cases in which the patients received roentgen therapy of the pituitary region, the posterior part of the orbits was also irradiated. The improvement in the state of the eyes following treatment may thus be ascribed partly to depression of the thyrotrophic hyperactivity of the pituitary and partly by the direct effect of the irradiation of the orbital tissue. In those cases in which the above-mentioned type of treatment did not produce satisfactory results roentgen treatment was extended to include roentgen irradiation of the anterior part of the orbits. This supplementary treatment may improve the results provided connective tissue proliferation behind the bulbs is not excessive.

In the treatment of acute, rapidly progressing eye symptoms, roentgen irradiation of the orbits only can produce dramatic improvement and should therefore be started without delay. This treatment, does not however, tackle the cause. Therefore it should be followed by irradiation of the pituitary region. The doses used produced no demonstrable undesired effect on the other functions of the hypophysis.

Early recognition of this type of Graves' disease is important and treatment should be started as soon as possible. Thyroidectomy, treatment with thiouracil compounds and radiotherapy of the thyroid glands are contra-indicated.

References.

- D'Angelo, S. A. and Gordon, A. S.: *Tr. Am. Goiter A.* 1949, p. 149. — Ashoo-Hansen, G. and Iversen, K.: *Acta endocrinol.* 8 (1951), 99. — Ashoo-Hansen, G., Iversen, K. and Wichmann, R.: *Acta endocrinol.* 11 (1952), 376. — v. Basedow, K. A.: *Wchschk. f. d. ges. Heilk.* 6 (1849), 197. — Beierwaltes, W.: *J. Clin. Endocrinol.* 11 (1951), 512. — Emsch, J.: *Strahlentherapie* 53 (1935), 73. — Brain, W., Russel and Savin, L. H.: *Tr. Ophth. Soc. U. Kingdom* 63 (1913), 1. — Burch, F. E.: *Minnesota Med.* 12 (1929), 668. — Cooper, A. C.: An introduction to clinical orbitonometry with special reference to intraorbital involvement in endocrinal disturbances. Leiden 1948. — Cooper, A. C.: The measurement of the retrobulbar resistance (orbitonometry) in the clinic. *Tr. Ophth. Soc. U. Kingdom* 67 (1949), 219. — McCullagh, E. P., Ruedemann, A. D. and Gardner, W. J.: *Tr. Am. A. Study Goiter* 1942-1946, p. 15. — Dobyns, B. M.: *J. Clin. Endocrinol.* 10 (1950), 192. — Friedgood, H. B.: *J. Clin. Endocrinol.* 1 (1941), 801. — Ginstburg, S.: *Ann. Int. Med.* 15 (1939), 421. — Graves, R. J.: *London Med. & Surg. J.* 7 (1835), 316. — Hermann, K.: *Brit. J. Ophth.* 36 (1952), 1. — Hertz, S., Means, J. H. and Williams, R. H.: *Western J. Surg. Obst. & Gynec.* 49 (1911), 493. — Jones, A.: *Brit. J. Radiol.* 24 (1951), 457. — Kaplan, I. L.: *Radiology* 35 (1941), 588. — Knudtzon, K.: *Acta psychiat. et neurol.* 24

- (1949), 523. — Kravitz, D. and Moshele, W.: *Am. J. Ophth.* 24 (1941), 527. — Loeb, L. and Bassett, R. B.: *Proc. Soc. Exper. Biol. & Med.* 27 (1939), 1940. — Loeb, L. and Friedmann, H.: *Proc. Soc. Exper. Biol. & Med.* 29 (1932), 648. — Lorenz, 1857: *Cit. Cooper, A. C.*: An introduction to clinical orbitonometry, with special reference to intra-orbital involvement in endocrinal disturbances. Leiden 1948. — Ludwig, A. W., Boas, N. F. and Seffer, L. I.: *Proc. Soc. Exper. Biol. & Med.* 73 (1950), 137. — Luft, R.: *Acta med. Scandinav.* 124 (1946), 227. — Luft, R.: *Nord. Med.* 38 (1948), 1065. — Mandeville, F. B.: *Radiology* 41 (1943), 268. — Marine, D. and Rosen, S. H.: *Proc. Soc. Exper. Biol. & Med.* 30 (1933), 901. — Means, J. H.: *Ann. Int. Med.* 23 (1945), 779. — Moore, R. Foster.: *Lancet* 20 (1929), 701. — Mulvany, J. H.: *Tr. Ophth. Soc. U. Kingdom* 63 (1943), 22. — Naffziger, H.: *Ann. Surg.* 94 (1931), 582. — Naffziger, H.: *Arch. Ophth.* 9 (1933), 1. — Parry, 1782: *Cit. Cooper, A. C.*: An introduction to clinical orbitonometry with special reference to intra-orbital involvement in endocrinal disturbances. Leiden 1948. — Paulson, D. L.: *Proc. Soc. Exper. Biol. & Med.* 36 (1937), 604. — Poppe, E.: *Acta radiol.* 23 (1942), 354. — Rasmussen, A. T. and Gardner, W. J.: *Endocrinology* 27 (1940), 219. — Rawson, R.: *J. Clin. Endocrinol.* 8 (1948), 826. — De Robertis, E. and Del Conte, E.: *Cit. De Robertis, E. J. Clin. Endocrinol.* 8 (1948), 956. — Schockaert, J. A.: *Am. J. Anat.* 49 (1932), 379. — Schwarz, G.: *Am. J. Roentgenol.* 55 (1946), 337. — Smelser, G. K.: *Am. J. Ophth.* 20 (1937), 1189. — Thomas, H. M. and Woods, A. C.: *Bull. Johns Hopkins Hosp.* 59 (1936), 99.
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Le Sphygmotonographie.

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K. CYVIN.

(Ce travail est parvenu à la rédaction le 12 Novembre 1953.)

Un grand nombre d'appareils plus ou moins exacts ont été construits pour l'enregistrement de la pression artérielle. Voici un appareil transportable très exact destiné aux recherches de la circulation sanguine au lit du malade. (Fig. 1.)

On comprime au moyen une poire l'air dans la boîte métallique jusqu'à une tension de presque une demi-atmosphère. Puis à l'aide d'un robinet à trois voies l'air est insufflé suivant deux circuits parallèles: Celui de la manchette anti-brachiale et celui de la manchette brachiale, ce dernier branché sur le manomètre à mercure enregistreur. Chaque circuit est pourvu d'un manomètre métallique et d'un sphygmoscope de Marey, l'un des sphygmoscopes étant à une membrane, et l'autre à quatre membranes superposées. Ces sphygmoscopes mettent en évidence les oscillations de la paroi artérielle. À l'aide de seringues à pistons micrométriques on peut régler la tension avec minutie. Par une série de serres micrométriques on peut faire gonfler à volonté les manchettes en déchargeant les sphygmoscopes par des serres correspondantes. Le manomètre à mercure compensateur, semblable à celui d'Uskoff (1908) enregistre la tension moyenne dans la manchette brachiale à l'aide d'un flotteur qui est traversé par l'air comprimé. Tous les tuyaux de communication sont en matière plastique.

Le pouls périphérique de l'avant bras, l'oscillogramme de la manchette brachiale et la tension présente dans celle-ci sont tracés par le polygraphe de Jaquet. (Fig. 2.) Par un robinet spécial on peut brancher instantanément un circuit enregistrant les sphygmogrammes simultanés de la carotide et de la fémorale, ainsi que la respiration.

Dans ce but j'ai construit des «porte-tambours» spéciaux (Fig. 1 b) à réglage micrométrique. Ces «porte-tambours» sont préférables aux «bras artificiels» ordinaires, parce qu'ils épousent mieux les mouvements minimes du membre.

La pression diastolique peut être déterminée suivant la manière formoscillatoire de v. Recklinghausen (1910). Une autre manière est celle de Gallavardin (1921),

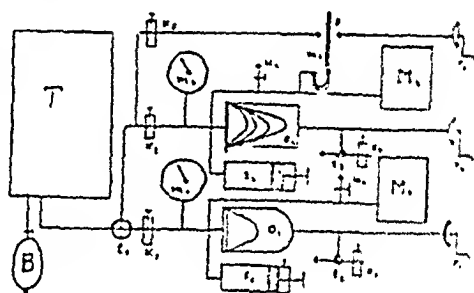
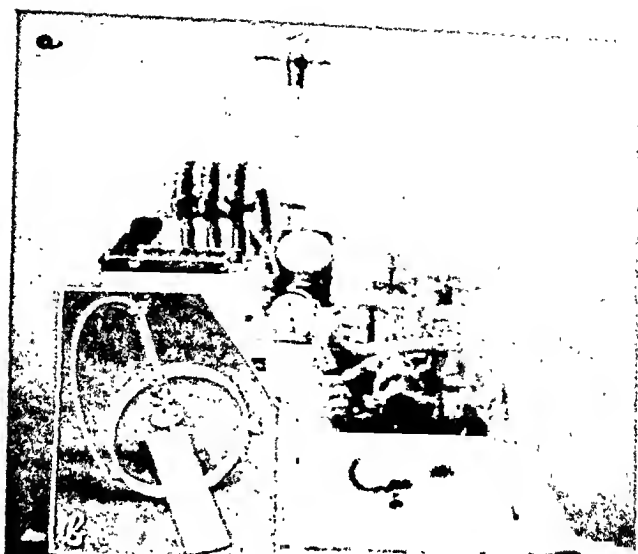


Fig. 1.

a. sphygmoténographe.

b. «porte-tambour» carotidien.

c. schéma:

B = poire, T = boîte métallique.

t = robinets à trois voies.

M₁ = manchette antibrachiale, M₂ = manchette brachiale.

m = manomètres, o = sphygmoscopes de Marey.

s = seringues, k = serres micrométriques.

m₂ = manomètre à mercure compensateur.

F = flotteur perforé.

r = tambours enregistreurs.

où la diminution du pouls périphérique indique la pression diastolique. La diminution des dernières pulsations périphériques indique la pression systolique. Le changement de la courbe anacrote en courbe catacrote en tant que signe de la pression systolique latérale de v. Recklinghausen sur l'oscillorhème de L. L. est moins constant. L'onde préanacrotique négative d'Erlanger (1921) en tant que signe de la pression diastolique a été constatée dans 98 % des cas étudiés avec le tambour enregistreur placé au-dessus de la cubitale.

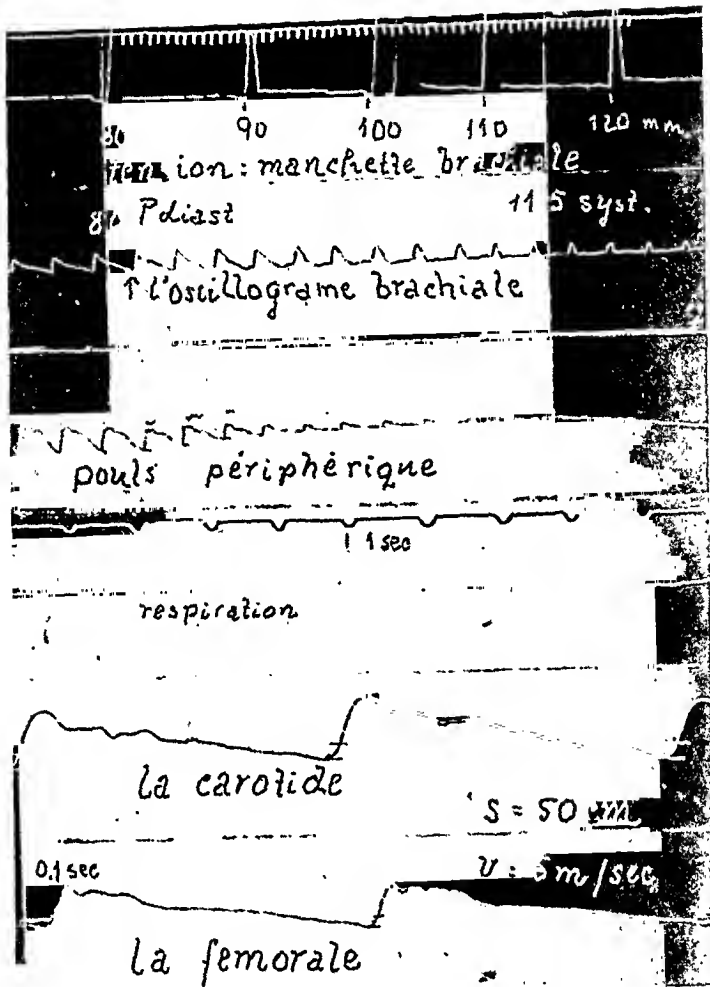


Fig. 2. Tracé obtenu par le sphygmotonomographe (1/1).

À l'aide d'une formule modifiée d'Apéria¹ (1941) on peut apprécier le débit ventriculaire (index cardiaque) ainsi que la résistance périphérique d'après la formule indiquée par Bazett (1935).

$$I = \frac{a \cdot l \cdot d}{v^2 \cdot s} \cdot c \quad R = \frac{3 \cdot Py}{I}$$

soit

I = index cardiaque = débit ventriculaire/surface du corps.

R = résistance périphérique.

a = amplitude = pression systolique ÷ pression diastolique.

l = longueur des vaisseaux mesurée depuis la première articulation costosternale gauche jusqu'au Poupart, augmentée de 10 cm.

d = diamètre aortique d'après Suter (1897).

v = vitesse de l'onde pulsatoire.

s = surface du corps d'après le tableau dressé par du Bois.

c = constante = 0.02 contenant

les coefficients compensateurs pour obtenir «I» en l/min/m² en exprimant «a» en mm Hg «l» en cm, «d» en cm² «v» en m/sec et «s» en m²,

puis une correction de la longueur totale des vaisseaux établie par Apéria,

la masse spécifique du sang

et le coefficient adaptant le produit au résultat trouvé par le procédé de Fick.

Py = pression moyenne.

L'appareil permet d'enregistrer quelques autres observations, soit les variations de la pression artérielle suivant les différentes conditions psychiques et physiques (Bickel, 1916), soit d'autres investigations sphymnographiques.

Summary.

A description is given of a portable sphymonograph well adapted for graphic registering of the systolic and diastolic blood pressure as well as respiration and pulse-wave velocity.

Bibliographie.

1. Uskoff, L.: Zeitschr. f. klin. Med. 66, 1908, p. 90. — 2. v. Recklinghausen, H.: Blutdruckmessung und Kreislauf. Dresden 1940. — 3. Gallavardin, L.: La tension artérielle en clinique. Paris 1921. — 4. Erlanger, J.: Amer. Journ. Physiol. 55, 1921, p. 51. — 5. Apéria, A.: Acta physiol. Scand. 2, 1941, p. 61. — 6. Bazett, H. C., Cotton, F. S., Laplace, L. B., Scott, J. C.: Amer. Journ. Physiol. 113, 1935, p. 312. — 7. Bickel, H.: Die wechselseitigen Beziehungen zwischen psychischem Geschehen und Blutdruck. Leipzig 1916. — 8. Suter, F.: Arch. f. exp. Pathol. 39, 1897, p. 289.
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Preliminary Report.

From the Medical Clinic of the University of Lund, Sweden.

On the Artificial Kidney XXVI.

Hypopotassaemia in General Hypothermia in Rabbits and its Control by Dialysis.

By

KAI C. NIELSEN.

(Submitted for publication Januari 11, 1954.)

Elliott and Crismon (1947), also Bigelow and collaborators (1950) found hyperpotassaemia in general hypothermia in rats and dogs, which was presumably of toxicologic significance.

This present experimental report refers to employment of the artificial kidney for simultaneous chilling of the blood of rabbits and correction of the expected hyperpotassaemia by dialysing the blood in vivo against suitably composed electrolyte solution of low temperature.

1. *Control experiments* (30 rabbits): Hypothermia was induced by means of a technique similar to the one employed by Kisch (1923), to raise the temperature of rabbits. Boerema and collaborators (1950) chilled dogs by cooling the blood in an extracorporeal system.

The blood was pumped by blood-pressure from arteria carotis, through a spiral-shaped glass tube, back to the vena jugularis. The tube lay immersed in icy cold water. After 108 ± 40 min. (Standard deviation) the rectal temperature of the animal had fallen to 23° C. and after 124 ± 53 min. to 22° C. In one experiment the temperature was, at its lowest, 19.5° , on the average $22.1 \pm 1.6^\circ$ C. Initial Nembutal narcosis. The frequency of respiration sank from 57 ± 21 to 10 ± 6 /min., pulse frequency from 304 ± 15 to 49 ± 8 /min. and the blood-pressure from 97 ± 15 to 37 ± 12 mm Hg.

Contrary to earlier reports in literature there was a significant decrease of serum potassium of 0.52 ± 0.12 mEq ($n = 14$). Serum calcium and protein as well as the hemoglobin revealed no significant changes.

2. *Experiments with the artificial kidney (Alwall's dialyser-ultrafilter). (15 rabbits): Normal serum potassium in hypothermia was maintained in these experiments. Dur-*

ing such bloodchilling, heparinization below some 30°C is usually unnecessary, i. e. the method does not involve risk of bleeding.

The possibility of lessening this risk in the dialysis of uremic patients with hypothermia, by lowering the temperature of the electrolyte solution (reduced heparinization) will be the object of future studies in this laboratory.

Summary.

In experiments with rabbits, hypothermia was induced through extracorporeal chilling of the blood in a spiral glass tube and in the artificial kidney respectively. In the latter series, the blood was dialysed against chilled electrolyte solution with normal potassium concentration.

The control experiments with the spiral glass tube revealed, in contrast to earlier reports in literature, a significant decrease of serum potassium by $0.52 \pm 0.12\text{ mEq}$ ($n = 14$).

In experiments with the artificial kidney normal serum potassium was maintained during hypothermia.

The investigation was carried out with the aid of a grant placed at the disposal of S. Alwall, M. D., from the Therese and Johan Andersson Memorial Foundation.

Literature.

Bigelow, W. G., Lindsay, W. K. and Greenwood, W. F.: *Ann. Surg.* **152**: 849, 1930. — Boerema, I., Wildschut, A. and Schmidt, W. J. H.: *Arch. chir. neerl.* **3**: 25, 1951. — Eberhart, H. W. and Crismon, J. M.: *Am. J. Physiol.* **151**: 356, 1917. — Kisch, B.: *Arch. exp. Phys.* **198**: 105, 1923.

Addendum: Since these experiments terminated, Swan and collab. (*Ann. Surg.* **157**: 360, 1953; *J. A. M. A.* **153**: 1081, 1953) have reported hypopotassaemia in hypothermia among dogs and human beings. During heart operations performed on patients at 21° to 26°C , ventricular fibrillation has been allayed by means of injections of potassium chloride.

The Third International Congress of Internal Medicine
will be held in Stockholm from the 15th to the 18th September 1954.

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Secretary General: Professor Anders Kristenson.

Two main subjects will be discussed at the congress:

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DEN 24. NORDISKA KONGRESSEN FÖR INVÄRTES MEDICIN.

Nordisk Förening för Invärtes Medicin avhåller sin 24. kongress i Riksbankens hus i Stockholm den 12—14 september 1954.

Söndagen den 12 september på kvällen samling och mottagning-fest.

Måndagen den 13 september kl. 9.30—12.30: Gemensamt sammanträde för Nordisk förening för klinisk kemi och klinisk fysiologi. Kl. 14.00—17.00: Fria föredrag.

Tisdagen den 14 september kl. 9.00—12.30: Fria föredrag. Kl. 14.00—17.00: Fria föredrag samt generalförsamling.

I omedelbar anslutning till den Nordiska kongressen avhålls den tredje Internationala kongressen för invärtes medicin, vilken tager sin början den 15 september kl. 10.30 och avslutas den 18 september kl. 15.30.

Preliminärt program och anmälningshandlingar för deltagande kommer att utsändas i vanlig tid före kongressen.

In der Zeit vom 9.—13. Juni 1954 findet in Berlin der

3. Deutsche Kongress für ärztliche Fortbildung

statt. An der wissenschaftlichen Gestaltung des Programms sind die Leiter der österreichischer, westdeutscher und Berliner Fortbildungsorganisationen betheilig.

Anfragen und Anmeldungen sind an das Büro der Kongressgesellschaft für ärztliche Fortbildung e. V., Berlin-Steglitz, Klingsorstrasse 29 zu richten.

From the Department of Metabolic Research, Wenner-Gren's Institute, and Ophthalmic Clinic, Karoline Institute, Stockholm, Sweden.

Plasma Lipids and Diabetic Retinopathy.

By

ANGELO IANNACCONE¹, ² and TORE KORNERUP.

(Submitted for publication September 15, 1953.)

A strikingly increased frequency of retinopathy in diabetic patients has become evident in the past decades (16), but the factors responsible for the development of this serious complication have not as yet been definitely established, and appear to require further study.

The observation that retinal vessels in diabetic retinopathy show fatty degeneration, which is most marked in the region of the capillary aneurysms, (1, 2) suggested a relationship between retinal disease and the blood lipid disturbance known to occur in diabetes mellitus. Attention was previously directed toward changes in serum cholesterol. Some observers reported higher cholesterol values in diabetic patients with retinopathy than in those without retinopathy, but others found no significant difference in these two groups. (5, 8, 15, 16, 20, 21). However, since measurement of cholesterol cannot be used as an accurate index of all lipid constituents, it is conceivable that the level of other blood lipids may be of more pertinence than cholesterol alone. Accordingly, the present study was undertaken to investigate the concentrations and interrelations of the principal plasma lipid fractions in diabetic retinopathy. A review of literature failed to reveal any similar investigation. Only Nastri and Malaguzzi Valeri (20) mentioned a higher mean value of total lipids in eighteen diabetics with retinopathy than in nine without retinopathy; but the data were not evaluated statistically and, since the greatest amount was found in a patient without retinopathy, the authors felt justified in attaching no importance to the difference between the two means. In a later paper of Cristini and Roversi (9) the levels of neutral fat and total lipids seem to be more elevated in ten diabetics with retinopathy and hepatomegaly than in diabetics showing neither retinopathy nor hepatomegaly, but this impression cannot be supported by statistical tests for reliability, because insufficient details are given concerning the latter patients.

¹ Swedish Government Fellow at the Department of Metabolic Research, Wenner-Gren's Institute, during the academic year 1952—53, while on leave of absence from the Institute of Medical Semiology, University of Naples, Italy.

² Dept. of Endocrinol., Mount Sinai Hosp., N. Y. 29.

While this study was under way, further interest in the relation of blood lipids to diabetic retinopathy was evoked by the finding of elevated values of the β_2 12-20 class of lipoproteins in the serum of diabetics with retinopathy (17), and by the stimulating hypothesis of Becker (3) and Friedenwald (12, 13) that in such patients there occurs a relative adrenal cortical hyperfunction with all the abnormalities of plasma lipids may be associated.

Material and Methods.

One hundred diabetic in-patients of the Swedish Diabetes Foundation Hospital at Stockholm were studied. No blood specimens for lipid analysis were as a rule obtained until at least seven days after the patients showed a good level of control of the disease, as judged by a feeling of well-being, normal weight, normal urine output, normal thirst and hunger, absence of ketonuria, moderate glycosuria and hyperglycemia, and freedom from insulin reactions. Before and during hospitalization the patients received an unmeasured normal diet, corresponding with that for healthy Swedish people; most of them were also given insulin. Women were never tested during the menstrual period. Diabetics with other conditions which might also affect the plasma lipids, such as thyroid and liver disease, the nephrotic syndrome, infections, xanthomatosis, were excluded from this investigation.

Venous blood was drawn into heparinized tubes on the morning after a fast of twelve to fourteen hours, and prior to insulin administration; the plasma was then separated by centrifugation.

Total lipids were determined by the Bram (6) gravimetric technique, which is basically similar to those recently used by others (10, 14). Some inaccuracy is admittedly involved in such gravimetric methods; however, as pointed out by Gertler and Oppenheimer (14), they are useful as a measure of difference between two groups of subjects. Total cholesterol determinations were made by a slightly modified Bloor method (4). Lipid phosphorus was determined by the Fiske-Subbarow technique (11) upon an alcohol-acetone extract of plasma (15). Values for plasma phospholipids may be obtained by multiplying the value for lipid phosphorus by 25. The cholesterol-lipid phosphorus ratios were calculated to the nearest first decimal place.

Analyses of each plasma specimen were run in duplicate. The reproducibility of the laboratory determinations is revealed by the following standard error of duplicate differences: 22 mg. per cent for total lipids, 4.9 mg. per cent for cholesterol, and 0.16 mg. per cent for lipid phosphorus.

The fundus examination was carried out by the direct image method. When no hemorrhages and exudates were seen in this way, the examination was repeated in monochromatic light ($\lambda = 575 \text{ m}\mu$) according to Kornerup (19). If no arterio-venous anastomoses, hemorrhages or exudates were found by this method, the fundus was then considered to be free from retinopathy. The presence of a single arterio-venous anastomosis or hemorrhage was sufficient for the diagnosis of retinopathy.

Table 1.
Plasma lipids in diabetic patients with retinopathy.

Case no.	Sex	Age (years)	Duration of diabetes (years)	Type of retinopathy	Total lipids (mg %)	Cholesterol (mg %)	Lipid phosphorus (mg %)	Cholesterol-lipid phosphorus ratio
1	M	17	11	Hemorrh.	1145	234	8.4	27.9
2	F	19	4	Hemorrh.	1085	273	8.3	32.9
3	F	20	16	Prolif.	700	192	6.6	29.1
4	F	20	17	Prolif.	1145	253	13.4	18.9
5	M	24	9	Hemorrh.	1140	269	13.8	19.5
6	M	25	14	Prolif.	1650	426	17.2	24.8
7	M	26	11	Exud.	1095	300	7.9	38.0
8	F	28	21	Prolif.	1675	365	14.4	25.3
9	F	28	15	Exud.	1091	390	11.0	35.5
10	F	33	8	Exud.	950	192	10.5	18.3
11	F	33	7	Exud.	1015	334	9.9	33.7
12	F	34	22	Exud.	1035	200	11.4	17.5
13	M	37	7	Prolif.	970	302	11.2	27.0
14	M	38	6	Exud.	1020	205	7.4	27.7
15	F	38	16	Hemorrh.	873	268	8.0	33.5
16	F	38	13	Hemorrh.	1340	374	12.6	29.7
17	F	40	18	Exud.	1095	279	8.8	31.7
18	M	41	12	Exud.	1430	485	14.6	33.2
19	F	43	19	Exud.	1055	317	11.8	26.9
20	F	44	10	Hemorrh.	1500	401	14.2	28.2
21	M	46	20	Exud.	1135	320	10.8	29.6
22	F	46	27	Exud.	1000	268	17.0	15.8
23	F	49	5	Exud.	1220	246	15.2	16.2
24	F	49	11	Exud.	1107	359	15.1	23.8
25	F	49	8	Exud.	1060	221	13.6	16.2
26	M	52	8	Hemorrh.	900	253	7.7	32.9
27	F	52	21	Exud.	800	196	8.1	24.2
28	M	55	8	Hemorrh.	1100	341	12.6	27.1
29	M	57	9	Exud.	1155	297	9.8	30.3
30	F	57	16	Exud.	1765	465	14.2	32.7
31	F	57	3	Exud.	950	255	8.5	30.0
32	M	60	24	Prolif.	1012	287	8.8	32.6
33	F	61	11	Exud.	960	295	11.7	25.2
34	M	65	8	Hemorrh.	782	225	15.8	14.2
35	F	65	9	Exud.	1250	283	13.1	21.6
36	F	65	16	Exud.	1350	335	14.3	23.4
37	M	66	4	Exud.	1145	205	8.7	23.6
38	M	67	20	Exud.	1080	253	8.1	31.2
39	F	67	15	Exud.	850	249	11.2	22.2
40	F	68	6	Hemorrh.	1235	370	11.1	33.3
41	F	73	12	Exud.	1055	286	20.0	14.3

The retinopathy was classified according to Hanum (15): hemorrhagic retinopathy: only aneurysms or hemorrhages present; exudative retinopathy: aneurysms or/and hemorrhages and exudates present; proliferative retinopathy: hemorrhages, exudates, new vessel formation and proliferation tissue present.

Results.

Diabetic retinopathy was found in 41 of the 100 patients who were investigated. 15 patients were male, 26 female; the ages ranged from 17 to 73 years; the duration of diabetes varied from 3 to 27 years (table 1). No evidence of diabetic re-

Table 2.

Plasma lipids in diabetic patients without retinopathy.

Case no.	Sex	Age (years)	Duration of diabetes (years) ¹	Total lipids (mg %)	Cholesterol (mg %)	Lip. 1 Phosphorus (mg %)	Cholesterol Phosphorus
1	F	15	0	850	285	9.1	23.1
2	F	16	5	1200	275	10.8	24.1
3	M	17	3	800	127	8.4	13.1
4	F	18	2	935	210	7.6	13.1
5	M	19	0	950	288	13.6	23.1
6	M	19	7	645	135	6.6	14.5
7	F	19	0	950	162	10.9	14.5
8	F	22	1	725	149	8.4	15.5
9	F	22	8	1150	298	12.6	17.5
10	M	24	9	865	260	7.5	20.5
11	F	24	0	930	217	6.5	13.1
12	F	24	0	690	211	8.2	20.1
13	M	25	10	750	171	7.2	13.5
14	M	27	0	1065	183	10.5	17.5
15	F	29	15	905	230	7.6	20.5
16	F	29	7	750	241	9.6	15.5
17	F	30	4	1375	231	13.2	15.5
18	M	32	3	835	205	9.6	22.5
19	F	32	0	610	223	9.8	22.5
20	F	32	2	775	115	6.0	19.5
21	F	34	9	1690	383	11.2	26.5
22	F	35	0	1145	274	12.6	21.5
23	F	36	7	850	250	7.1	15.5
24	F	38	1	1330	292	9.5	23.5
25	F	39	0	1030	250	10.6	18.5
26	M	40	13	900	167	9.5	14.5
27	F	40	0	815	394	11.3	24.5
28	F	41	27	950	191	11.6	16.5
29	F	41	7	1150	212	11.6	21.5
30	F	42	1	1025	215	13.6	17.5
31	M	43	9	810	253	9.1	22.5
32	M	43	3	890	174	7.1	11.5
33	M	45	0	950	383	9.2	22.5
34	M	45	6	1320	291	13.2	21.5
35	M	46	13	1230	259	11.4	20.5
36	M	46	0	1320	320	10.9	21.5
37	M	47	0	785	265	9.9	14.5
38	F	47	0	813	260	8.1	21.5
39	M	48	0	800	384	19.8	22.5
40	F	49	0	1150	433	13.7	18.5
41	F	50	11	1697	276	14.5	24.5
42	M	51	5	705	321	8.5	14.5
43	M	51	2	975	151	12.6	15.5
44	F	52	0	970	212	10.6	20.5
45	F	51	0	655	152	6.2	13.5
46	M	55	9	1115	272	16.9	14.5
47	F	55	0	1355	190	17.2	21.5
48	F	56	0	925	399	8.4	21.5
49	M	56	0	1065	322	7.5	13.5
50	F	59	1	1525	266	20.6	22.5
51	M	59	0	1655	459	17.6	24.5
52	F	60	2	1590	411	12.5	24.5
53	F	61	14	850	291	12.7	13.5
54	F	61	0	875	379	10.1	14.5

¹ 0 years means less than 1 year; 1 year means from 1 year to less than 2 years, etc.

Case no.	Sex	Age (years)	Duration of diabetes (years)	Total lipids (mg %)	Cholesterol (mg %)	Lipid phosphorus (mg %)	Cholesterol-lipid phosphorus ratio
55	F	66	4	995	322	12.9	25.0
56	M	67	4	1005	237	16.6	14.3
57	F	67	8	930	333	8.2	40.6
58	M	75	6	690	168	8.3	20.2
59	F	77	0	1415	342	14.1	24.3

Table 3.

Means and their standard deviations and standard errors of plasma lipid values in diabetic patients with and without retinopathy.

		Total lipids (mg %)	Cholesterol (mg %)	Lipid phosphorus (mg %)	Cholesterol-lipid phosphorus ratio
Patients with retinopathy (41 cases)	Mean	1120	294	11.6	26.3
	Standard deviation	231.5	73.2	3.16	6.40
	Standard error	36.2	11.4	0.49	1.00
Patients without retinopathy (59 cases)	Mean	1002	263	10.7	25.5
	Standard deviation	248.2	83.8	3.10	7.94
	Standard error	32.3	10.9	0.40	1.03

tinopathy was exhibited by the remaining 59 subjects (23 males and 36 females), aged 15 to 77 years, with a duration of diabetes from a few months to 27 years (table 2).

The means, and their standard deviations and standard errors of lipid values obtained in each group of patients are recorded in table 3. Mean cholesterol, mean lipid phosphorus, and mean cholesterol-lipid phosphorus ratio were higher in subjects with retinopathy than in those without retinopathy; the differences, however, are not statistically significant ($P > 0.05$). The average amount of total lipids was also greater in patients with than without retinopathy; this difference is statistically significant ($P < 0.05$).¹

In neither group did lipid levels appear to be related to the age of the patients or to the duration of diabetes.

Comment.

The finding that plasma cholesterol concentration of diabetics with retinopathy is not significantly increased in comparison with diabetics without retinopathy, is in agreement with other published observations (5, 15, 20). In addition, our study shows that the plasma lipid phosphorus level and the cholesterol-lipid phosphorus ratio are statistically equal in both groups, while the mean total lipids are significantly higher in diabetics with retinopathy. The question as to what lipid fractions may actually account for the difference in total lipids cannot,

¹ Standard errors and « P » values were calculated according to Snedecor (23).

however, be definitely answered by the data presented here, and would require further investigation.

The significance of the elevation of plasma total lipids in diabetes with retinopathy is difficult to assess. Of particular interest in this connection is the above mentioned hypothesis of Beeker and Friedenwald that the retinopathy of the diabetic patients may be due to an increased secretion of cortisone or related substances (3, 12, 13). Administration of cortisone to normal rabbits leads, in fact, to a marked degree of lipemia with a rise of serum fatty acids (18, 22). Moreover, alloxan diabetic rabbits injected with ACTH or cortisone show lesions resembling early diabetic retinopathy (3, 13). On the other hand, as emphasized by Friedenwald (13), lipemia does not readily result from cortisone treatment in rats; these animals also fail to exhibit retinal capillary aneurysms under the experimental conditions that produce such alterations in rabbits. Our finding that total lipids are higher in the plasma of diabetes with retinopathy might then be related to increased adrenal cortical activity in these patients.

Summary.

Total lipids, cholesterol, lipid phosphorus and cholesterol-lipid phosphorus ratio were determined on the blood plasma of 41 diabetes with retinopathy and 59 diabetes without retinopathy. A significant elevation of plasma total lipids was found in diabetes with retinopathy. This observation is discussed in relation to the recent hypothesis of increased adrenal cortical activity in diabetic patients showing retinopathy.

We express our gratitude to Med. Dr. Jakob Möllerström for the laboratory facilities offered us at the Department of Metabolic Research, Wenner-Gren Institute, and for opportunities to study patients at the Swedish Diabetes Foundation Hospital.

References.

- 1) Ashton, N.: *Proc. Roy. Soc. Med.* **44**, 747, 1951. — 2) Ballantyne, A. J. and Loewenstein, A.: *Trans. Ophth. Soc. U. Kingdom* **63**, 95, 1943. — 3) Beeker, B.: *Ann. int. Med.* **37**, 273, 1952. — 4) Bloor, W. R., Pelkan, K. F. and Allen, D. M.: *J. Biol. Chem.* **52**, 191, 1922. — 5) Boek, R. H.: *Arch. Ophth.* **29**, 919, 1943. — 6) Brun, G.: *Bibl. f. Læger* **131**, 197, 1939. — 7) Brun, G.: *Bibl. f. Læger* **131**, 203, 1939. — 8) Campos, C. A. and Molina, E. E.: *Prensa Méd. Argent.* **34**, 405, 1947. — 9) Cristini, G. and Roversi, L.: *Acta Ophth.* **27**, 563, 1949. — 10) Eilert, M. L.: *Metabolism* **2**, 137, 1953. — 11) Fiske, C. H. and Subbarow, Y.: *J. Biol. Chem.* **66**, 375, 1925. — 12) Friedenwald, J. S.: *J. A. M. A.* **150**, 969, 1952. — 13) Friedenwald, J. S.: *Diabetes* **2**, 237, 1953. — 14) Gertler, M. M. and Oppenheimer, B. S.: *Circulation* **7**, 533, 1953. — 15) Hanum, S.: *Acta Ophth., Suppl.* **XVI**, 1938. — 16) Joslin, E. P.: *The treatment of diabetes mellitus*. 8th Ed. Lea & Febiger, Philadelphia, 1946. — 17) Keiding, N. R., Mann, G. V., Root, H. F., Lawry, E. Y. and Marble, A.: *Diabetes* **1**, 434, 1952. — 18) Kobernick, S. D. and More, R. H.: *Proc. Soc. Exp. Biol. & Med.* **74**, 602, 1950. — 19) Kornerup, T.: *Acta Ophth., Suppl.* **XXVIII**, 1947. — 20) Nastri, F. and Malaguzzi Valeri, C.: *XV Cong. Ophth.* **4**, 175, 1937. — 21) Quiroz, J. A. and Iturbe, I.: *An. Soc. Mex. de Oftal.* **23**, 1, 1949. — 22) Rich, A. R., Cochran, T. H. and McGoon, D. C.: *Bull. Johns Hopk. Hosp.* **88**, 101, 1951. — 23) Snedecor, G. W.: *Statistical Methods*. 4th Ed. Iowa State College Press, 1950.

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Plasma Lipids and Diabetic Atherosclerosis.

By

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(Submitted for publication September 15, 1953.)

The importance of deviations in the serum lipids for the genesis of experimental atherosclerosis, and the tendency of diabetic patients to show hyperlipemia suggested that aberrations of blood lipids might account for the frequent occurrence of atherosclerosis in diabetes mellitus. However, while some investigators (2, 18, 19) observed higher cholesterol concentrations in diabetics with atherosclerosis than in diabetics without atherosclerosis, others (3, 11, 13, 14, 17) failed to confirm these findings. Similarly, it was both affirmed (2) and denied (3, 9, 13) that an evident relationship exists between the level of certain blood lipoproteins and the incidence of atherosclerosis in diabetic patients.

Following the demonstration that phospholipids exert a stabilizing effect on the other blood lipids and an increased serum cholesterol-phospholipid ratio appears to favour the development of cholesterol atherosclerosis in the rabbit (1, 5, 16), attention was also given to the ratio of serum cholesterol to phospholipids. Pomeranze and Kunkel (18) reported, in fact, higher cholesterol-phospholipid ratios in 25 diabetic patients with severe atherosclerosis than in 25 with moderate or no atherosclerosis. In addition, they found a higher percentage of diabetics with severe atherosclerosis to have total lipid levels above 750 mg per cent. Since we studied the plasma lipid pattern in a somewhat larger series of patients and our conclusions are not in keeping with those of Pomeranze and Kunkel, it seemed worth while to publish our results.

Material and methods.

Total plasma lipids, total cholesterol, lipid phosphorus and cholesterol-lipid phosphorus ratio were determined in 35 unselected diabetics with definite evidence

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of atherosclerosis and 35 unselected diabetics without manifest atherosclerosis. All subjects used for the present investigation were in-patients of the Hospital of the Swedish Diabetes Foundation at Stockholm.

Criteria for the diagnosis of atherosclerosis were: a typical history of myocardial infarction, clinical and electrocardiographic signs of coronary insufficiency, gangrene of the feet, or unequivocal evidence of atherosclerotic change in the ocular fundi. The patients considered to have no manifest atherosclerosis all showed no history and no physical signs or symptoms of coronary disease, of peripheral arterial disease or of cerebrovascular accidents, normal electrocardiogram, no retinal sclerosis, no radiographic vascular calcification in the lower extremities, normal oscillometric readings, and normal skin temperature of the toes as measured by a thermocouple. However, since atherosclerosis may occur without symptoms or signs, it is recognized that subjects with hidden atherosclerosis may be clinically classified as free from atherosclerosis (10, 18, 21). As pointed out by Gould (8), comparisons of living individuals with and without atherosclerosis are actually comparisons between different anatomic localizations and different degrees of severity of atheromatous lesions.

Metabolic conditions of the patients at the time of blood collection and methods for lipid analysis were the same as described in a previous communication from this Department (12).

Double analyses of each plasma specimen were made and the following standard errors of duplicate differences¹ were obtained: mg 19.7 per cent for total lipids, mg 6.6 per cent for cholesterol, and mg 0.14 per cent for lipid phosphorus.

Results.

The values for total lipids, cholesterol, lipid phosphorus and cholesterol-lipid phosphorus ratio in each patient are indicated in tables 1 and 2.

The mean values are recorded in table 3 along with their standard deviations and standard errors. All average values were higher in diabetics with atherosclerosis than in diabetics without atherosclerosis, but none of the differences is statistically significant ($P > 0.05$).

Since a sex difference has been claimed to occur in the levels of plasma lipids of normal subjects (7), the diabetics studied were subdivided according to sex, and patients of the same sex were compared (table 4). No difference in plasma total lipids, cholesterol, lipid phosphorus or cholesterol-lipid phosphorus ratio was apparent between male diabetics with and without atherosclerosis. Female diabetics with atherosclerosis showed statistically higher values of plasma cholesterol and total lipids than female diabetics without atherosclerosis, while lipid phosphorus and cholesterol-lipid phosphorus ratio were not significantly different.

In the present material atherosclerosis was more frequent in older diabetics (fig. 1). Since in health and coronary artery disease there is a tendency for increased

¹ Standard error of duplicates = $\sqrt{\frac{\sum d^2}{2K}}$, where d = difference between duplicate analyses, and K = number of pairs.

Table 1.

Plasma lipids in diabetic patients with atherosclerosis.

Case no.	Sex	Age (years)	Duration of diabetes (years) ¹	Total lipids (mg %)	Cholesterol (mg %)	Lipid phosphorus (mg %)	Cholesterol-lipid phosphorus ratio
1	M	24	9	1,140	269	13.8	19.5
2	M	38	6	1,020	205	7.4	27.7
3	F	38	16	873	268	8.0	33.5
4	M	40	13	900	167	9.3	18.0
5	F	42	1	1,095	225	13.0	17.3
6	F	44	10	1,500	401	14.2	28.2
7	M	46	20	1,135	320	10.8	29.6
8	M	46	0	1,320	320	10.9	29.4
9	F	47	0	843	260	8.4	31.0
10	M	48	0	800	384	10.8	35.6
11	F	49	0	1,150	513	15.1	34.0
12	M	51	5	705	321	8.8	36.5
13	M	52	8	900	253	7.7	32.9
14	F	52	0	960	212	10.6	20.0
15	F	54	0	655	152	6.8	22.4
16	M	55	8	1,100	341	12.6	27.1
17	F	56	1	1,005	322	7.8	41.3
18	M	57	9	1,155	297	9.8	30.3
19	F	57	16	1,765	465	14.2	32.7
20	F	57	3	950	255	8.5	30.0
21	M	59	0	1,525	206	20.0	10.3
22	F	59	2	1,655	459	17.9	25.6
23	M	60	24	1,012	287	8.8	32.6
24	F	60	18	1,500	411	12.2	33.7
25	F	64	0	865	339	10.7	31.7
26	M	65	8	782	225	15.8	14.2
27	F	65	9	1,250	283	13.1	21.6
28	F	65	16	1,350	335	14.3	23.4
29	M	66	4	1,145	205	8.7	23.6
30	F	67	8	930	333	8.2	40.6
31	F	67	15	850	249	11.2	22.2
32	F	68	6	1,235	370	11.1	33.3
33	F	73	12	1,055	286	20.0	14.3
34	M	75	6	690	168	8.3	20.2
35	F	77	0	1,415	342	14.1	24.3

serum lipid concentrations with age (6, 7, 15), the observed difference in plasma cholesterol and total lipids between female diabetics with and without atherosclerosis may actually be due to their different ages. In fact, if a group of female diabetics with atherosclerosis is contrasted with a group of female diabetics of comparable age without atherosclerosis, no significant difference in any of the plasma lipid fractions is evident between the two groups (table 5).

Comment.

The data presented in this paper indicate that no significant difference in plasma total lipids, cholesterol, lipid phosphorus or cholesterol-lipid phosphorus ratio appears to exist between diabetics with and without atherosclerosis. Of interest in

¹ «0 year» means «less than 1 year», «1 year» means «from 1 year to less than 2 years», and so on.

Table 2.
Plasma lipids in diabetic patients without atherosclerosis.

Case no.	Sex	Age (years)	Duration of diabetes (years) ¹	Total lipids (mg %)	Cholesterol (mg %)	Lipid phosphorus (mg %)	Cholesterol-lipid phosphorus ratio
1	F	15	2	850	285	9.1	31.3
2	M	17	11	1,145	242	8.8	27.5
3	F	18	2	995	240	7.0	34.3
4	M	19	0	950	288	13.0	22.2
5	F	19	0	960	162	10.9	14.9
6	F	22	1	735	149	8.4	17.7
7	F	22	8	1,150	298	12.6	23.7
8	M	24	9	865	290	7.3	39.7
9	F	24	0	690	211	8.3	25.4
10	M	25	10	750	171	7.2	23.8
11	M	27	0	1,065	183	10.3	17.8
12	F	28	15	1,091	390	11.0	35.5
13	F	29	15	906	230	7.6	30.3
14	F	32	0	640	223	9.8	22.8
15	F	32	2	775	115	6.0	19.2
16	F	33	8	950	192	10.5	18.3
17	F	34	22	1,035	200	11.4	17.5
18	F	35	0	1,145	274	12.6	21.7
19	F	36	7	1,330	292	9.5	30.7
20	F	38	1	850	250	7.1	35.2
21	F	39	0	1,030	250	10.6	23.6
22	F	40	0	815	394	11.5	34.3
23	M	41	12	1,430	485	14.6	33.2
24	F	41	27	960	191	11.6	16.5
25	M	43	3	890	174	7.4	23.5
26	M	45	0	950	383	9.2	41.6
27	M	45	6	1,320	291	13.2	22.0
28	M	46	13	1,230	250	11.4	21.9
29	F	49	11	1,107	359	15.1	23.8
30	F	49	8	1,060	221	13.6	16.2
31	M	52	14	1,390	293	14.2	20.6
32	F	55	0	1,355	199	17.2	11.6
33	F	60	14	890	394	12.6	31.3
34	F	60	11	960	295	11.7	25.2
35	M	67	4	1,005	237	16.6	14.3

this connection is the work of Stamler (22), who reported that a fall in the cholesterol-phospholipid ratio does not prevent aorta atherosclerosis in stilbesterol-treated cockerels. Recently Katz et al. (13) found no significant difference between the cholesterol-phospholipid ratio of non-diabetic patients with coronary artery disease and normal controls.

Our observations also emphasize the importance of taking into account the age and sex of patients when data on plasma lipids are being evaluated.

It will be seen from tables 1, 2 and 3 that both diabetics with atherosclerosis and diabetics without atherosclerosis may show elevated or low levels of total lipids, cholesterol, lipid phosphorus and cholesterol-lipid phosphorus ratio in the plasma. Therefore none of these measurements can be used as a discriminator between diabetics with and without atherosclerosis.

¹ «0 year» means «less than 1 year», «1 year» means «from 1 year to less than 2 years», and so on.

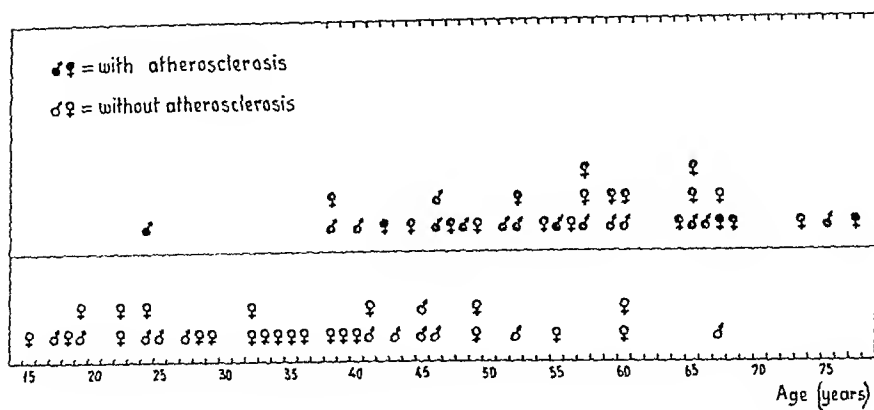


Fig. 1. Distribution of the patients according to age. Each symbol represents one patient.

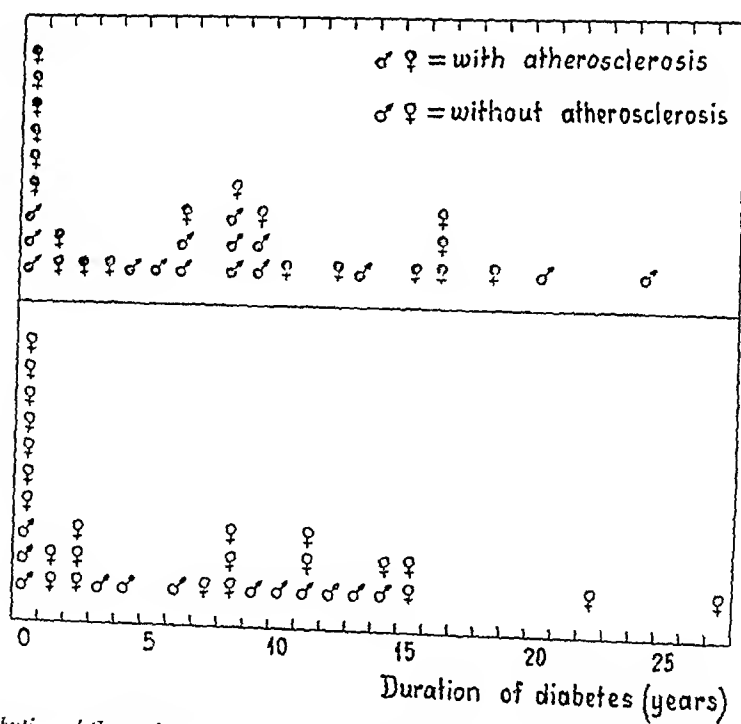


Fig. 2. Distribution of the patients according to the duration of diabetes mellitus. Each symbol represents one patient.

Table 3.

Statistical significance of the differences between the means of plasma lipid values in diabetic patients with and without atherosclerosis.

	Total lipids	Cholesterol	Lipid phosphorus	Cholesterol-lipid phosphorus ratio
	(mg %)	(mg %)	(mg %)	
First group: Patients with atherosclerosis (35 cases)	Mean 1,092	299	11.5	27.1
	Standard deviation 278.4	86.6	3.47	7.55
	Standard error ... 47.1	14.6	0.59	1.28
Second group: Patients without atherosclerosis (35 cases)	Mean 1,008	260	10.8	24.8
	Standard deviation 200.8	81.4	2.83	7.57
	Standard error ... 33.9	13.7	0.48	1.28
Differences between the means of the first and the second group	+ 84	+ 39	+ 0.7	+ 2.3
t^1	1.448	1.942	0.924	1.272
P^1	> 0.05	> 0.05	> 0.05	> 0.05

As already noted, in our series the incidence of atherosclerosis was higher in older diabetics (fig. 1), while the duration of clinical diabetes mellitus was similar in diabetics with and without atherosclerosis (fig. 2). This contrasts with the widespread opinion that the duration of diabetes is the most important factor in the development of atherosclerosis in diabetics (4). However, our findings are consistent with the data of Semple (20), who observed that the occurrence of peripheral arterial disease in diabetics was related to increasing age but not to the duration of the diabetes.

Summary.

Plasma total lipids, cholesterol, lipid phosphorus and cholesterol-lipid phosphorus ratio were determined in 35 unselected diabetics with evidence of atherosclerosis and 35 unselected diabetics without manifest atherosclerosis. No significant difference was found between the two groups.

The importance of considering the age and sex of patients when plasma lipid values are being interpreted, is stressed.

In the present series increasing age appears to be a more important factor than the duration of the diabetes in the development of atherosclerosis.

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¹ t and P values were calculated according to Snedecor, G. W.: Statistical Methods. Iowa College Press, 1950.

Table 4.

Statistical significance of the differences between the means of plasma lipid values in diabetic patients with and without atherosclerosis divided according to sex.

A) FEMALES					
		Total lipids	Cholesterol	Lipid phosphorus	Cholesterol-lipid phosphorus ratio
		(mg %)	(mg %)	(mg %)	
First group: Patients with atherosclerosis (20 cases)	Mean	1,145	324	12.0	28.1
	Standard deviation	303.6	92.5	3.52	7.34
	Standard error ...	67.9	20.7	0.78	1.64
Second group: Patients without atherosclerosis (23 cases)	Mean	969	253	10.7	24.4
	Standard deviation	182.7	77.6	2.68	7.26
	Standard error ...	38.1	16.2	0.56	1.51
Differences between the means of the first and the second group		+ 176	+ 71	+ 1.3	+ 3.7
<i>t</i>		2.337	2.737	1.373	1.659
<i>P</i>		< 0.03	< 0.01	> 0.05	> 0.05
B) MALES					
		Total lipids	Cholesterol	Lipid phosphorus	Cholesterol-lipid phosphorus ratio
		(mg %)	(mg %)	(mg %)	
First group: Patients with atherosclerosis (15 cases)	Mean	1,022	265	10.9	25.8
	Standard deviation	232.2	66.6	3.43	7.89
	Standard error ...	60.0	17.2	0.88	2.04
Second group: Patients without atherosclerosis (12 cases)	Mean	1,082	274	11.1	25.7
	Standard deviation	220.3	90.1	3.17	8.37
	Standard error ...	63.7	26.0	0.91	2.41
Differences between the means of the first and the second group		- 60	- 9	- 0.2	+ 0.1
<i>t</i>		0.682	0.299	0.155	0.031
<i>P</i>		> 0.05	> 0.05	> 0.05	> 0.05

References.

1. Ahrens, E. H. and Kunkel, H. G.: J. Exper. Med. 90, 409, 1949. — 2. Barach, J. H. and Lowy, A. D.: Diabetes 1, 441, 1952. — 3. DeWind, L. T., Michaels, G. D. and Kinsell, L. W.: Ann. int. Med. 37, 344, 1952. — 4. Dolger, H.: in «Progress in Clinical Endocrinology», edited by S. Soskin. Grune & Stratton, New York, 1950. Pag. 303. — 5. Duff, G. L. and Payne, T. P. B.: J. Exper. Med. 92, 299, 1950. — 6. Gertler, M. M., Garn, S. M. and Bland, E. F.: Circulation 2, 517, 1950. — 7. Gertler, M. M. and Oppenheimer, B. S.: Circulation 7, 533, 1953. — 8. Gould, R. G.: Am. J. Med. 11, 209, 1951. — 9. Hanig, M. and Lauffer, M. A.: Diabetes 1, 447, 1952. — 10. Herzstein, J. and Weinroth, L. A.: Arch. int. Med. 76, 34, 1945. — 11. Hunt, H. M.: New Eng. J. Med. 201, 659, 1929. —

Table 5.

Statistical significance of the differences between the means of plasma lipid values in female diabetics of comparable age (ranging from 38 to 60 years).

		Total lipids	Cholesterol	Lipid phosphorus	Cholesterol-lipid phosphorus ratio
		(mg %)	(mg %)	(mg %)	
First group: Patients with atherosclerosis (12 cases)	Mean	1,163	329	11.4	29.1
	Standard deviation	355.8	117.1	3.55	6.81
	Standard error ...	102.8	33.8	1.02	1.96
Second group: Patients without atherosclerosis (9 cases)	Mean	1,003	284	12.3	24.2
	Standard deviation	163.5	80.7	2.85	8.34
	Standard error ...	54.5	26.9	0.95	2.78
Differences between the means of the first and the second group		+ 160	+ 45	- 0.9	+ 4.9
<i>t</i>		1.248	0.986	0.625	1.485
<i>P</i>		> 0.05	> 0.05	> 0.05	> 0.05

12. Iannaccone, A. and Kornerup, T.: *Acta Med. Scand.* 148, 411, 1954. — 13. Katz, L. B., Rhodes, G. J., George, R. S. and Moses, C.: *Am. J. Med. Sc.* 225, 120, 1953. — 14. Keiding, N. R., Mann, G. V., Root, H. F., Lawry, E. Y. and Marble, A.: *Diabetes* 1, 434, 1952. — 15. Keys, A., Mickelsen, O., Miller, E. v. O., Hayes, E. R. and Todd, R. L.: *J. Clin. Investigation* 29, 1347, 1950. — 16. Ladd, A. T., Kellner, A. and Correll, J. W.: *Fed. Proc.* 8, 360, 1949. — 17. Man, E. B. and Peters, J. P.: *J. Clin. Investigation* 14, 579, 1935. — 18. Pomeranze, J. and Kunkel, H. G.: *Proc. Am. Diab. Ass.* 10, 217, 1950. — 19. Rabinowitch, I. M.: *Arch. int. Med.* 43, 363, 1929. — 20. Semple, R.: *Lancet* 1, 1064, 1953. — 21. Spain, D. M., Bradess, V. A. and Huss, G.: *Ann. int. Med.* 38, 254, 1953. — 22. Stamler, J.: *Med. Clin. North Am.* 36, 177, 1952.

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Studies in the Utilization of Pentoses in Diabetes.

By

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(Submitted for publication, September 15, 1953.)

At the turn of the century numerous authors made pioneer studies on pentoses with reference to man and animals. On many major questions no agreement could be reached, and many features remained unsolved. Consequently the interest in the pentose problem abated, and not until about 1930 was the matter taken up again, by Grafe and his co-workers. In the course of their very extensive investigations they studied xylose, the wood-sugar with regard to its reactions in persons with normal metabolism and in diabetics. Here, Grafe came to the conclusion that both the normal and the diabetic organism react in the same way when supplied with xylose. Resorption and digestibility are very good. The metabolism of pentose progresses independently of that of dextrose. A small part of the xylose remaining in the body is retained, whereas the main amount is combusted to a considerable extent — a process which was clearly established by Marble and Strieck, during their extensive respiration-tests, by the steady and distinct rise of the respiratory quotient. In the most serious cases of diabetes, xylose was almost the only nutrient which caused the quotients to rise considerably. Using starving dogs Magendantz showed, by the distinctly falling excretion of nitrogen, the sparing action of xylose on protein-destruction. In this connection, he was in no case able to prove increased formation of glycogen in the liver, following the method of Pflüger. From these investigations Grafe came to the conclusion that xylose is an excellent substitute for dextrose for the diabetic.

Various reasons led us to take up once again the problem of pentose during the past three years. On the one hand all vegetable food contains varying amounts of pentoses or of pentosans, their polymerization-products, which we take daily in our food. The question of utilization in relation to the importance of vegetables

in the diet for diabetes therefore seemed us all the more interesting and essential. On the other hand the influence of pentose on the intermediary metabolism had to be investigated further if it were to be considered as a dietary sugar-substitute. All our experiments were carried out with d-xylose with which we were supplied by the Carbon Chemical Works at Lübeck.

The degree of sweetness of xylose as estimated after the method of Paul, is 0.67 if that of saccharose is 1. The comparative degree of sweetness of dextrose is 0.53 and that of sorbitol is 0.43. Xylose is therefore 58 per cent sweeter than the wellknown sorbitol.

We started our investigations with animal tests. In all, 104 rats in different groups were fed for a year, with 5 to 10 per cent xylose added to their normal diet. The increases in weight and the state of their fur were better than in the control animals. This is explained by the fact that pentoses comprise up to 25 per cent of the dry weight of food of herbivorous animals. Special attention was given to eyes and kidneys but in no case were there any pathological findings. Contrary to this, the American Matchett from the United States Department of Agriculture reported in 1951 on cataract development after feeding test-animals on xylose. However, the kind of animal, duration of test, and doses are not stated. We do not think that our term of research of one year is too short when one considers that a rat will live up to two years. Moreover, our findings were confirmed in the second and third generation of test-animals.

After the introductory animal tests we checked the behaviour of xylose in persons with normal metabolism. As long as amounts of 40 grams as a single dose or of 80 grams as a total daily dose were not exceeded, we found as a rule good digestibility without symptoms in the normal persons examined by us. Larger doses may result in laxative effects of short duration, in connection with which individual fluctuations appear which cannot be explained. Likewise, we were never able to prove pentose excretion via the intestinal tract. A part of the administered xylose is however always excreted in the urine. In the case of persons with normal metabolism we found an average excretion of xylose of 15 per cent. The post excretion lasted thirty-six hours at the longest. The following table shows the proportion excreted in nine healthy subjects who were given a daily single dose of 40 grams of xylose for a week.

The regular xylose excretion after the most different dosages seems to be dependent on a low renal threshold for this sugar. In 1933, Fishberg and Friedfeld established by means of extensive material that the normal kidney is able to concentrate up to a urinary level of 2.5 per cent in two hours after administration of 50 grams of xylose, and excretes up to 25 per cent of the total ingestion within 24 hours. When the renal function is not intact these values always lie considerably lower and the pentose level in blood is higher than normal. Since, according to Fishberg and Friedfeld this excretion test with xylose is valuable for the diagnosis of renal functional disturbances in diabetes, we also occupied ourselves with this question and were able to obtain confirmation of the concentration circumstances for xylose. This will be reported elsewhere, however.

Another interesting aspect is the behaviour of blood sugar after xylose ad-

Table 1.

Nine persons of both sexes with normal metabolism, given a daily dose of 40 grams for a week. The minimum of xylose excretion lies around 9.5 per cent, the maximum around 19.5 per cent. The average excretion, therefore, amounts to about 15 per cent. No dyspeptic troubles, no change in state of stool. In the case of increased doses over several weeks, the utilization is slightly worse.

Pentose Excretion in g by normal test subjects after intake of 40g Xylose.								Mean pro die	
	1.Day	2.Day	3.Day	4.Day	5.Day	6.Day	7.Day	g	%
E.T. 27years ♀	5.94	5.2	8.68	6.1	4.57	5.85	6.5	6.1	15.3
G.B. 41 " ♀	2.4	4.55	3.95	3.68	4.85	2.3	5.0	3.8	9.5
D.W. 39 " ♀	6.3	6.1	5.88	5.5	6.0	5.2	6.3	5.9	14.8
E.P. 62 " ♂	3.8	5.54	6.96	8.65	5.49	4.76	6.1	5.9	14.8
C.K. 71 " ♂	3.3	7.04	6.26	6.2	7.97	8.2	7.7	6.7	16.8
H.J. 65 " ♂	5.75	6.4	8.64	8.6	6.49	10.48	8.19	7.8	19.5
M.L. 31 " ♂	4.99	4.43	7.1	6.33	5.94	5.13	6.4	5.8	14.5
G.O. 24 " ♀	5.15	4.8	6.95	6.5	7.57	6.3	6.17	6.2	15.5
L.A. 51 " ♀	4.55	5.7	6.75	5.6	6.6	5.35	6.1	5.8	14.5
Excretion Minimum: 3.8 g = 9.5 %								Mean Excretion: 6.0g = 15 %	
» Maximum: 7.8 g = 19.5 %									

ministration. Invariably a rise was established which was, however, always caused by pentose. The normal pentose level in blood in a healthy person is 10 to 30 milligrams per cent and may rise up to 70 milligrams per cent, depending on the size of the dose.

In the course of the clinical treatment of 63 diabetics, we have now examined the utilization of xylose and its influence on carbohydrate metabolism. There was no essential difference between these and healthy persons with regard to all features previously mentioned, namely good digestibility without disturbing symptoms on ingestion of 40 grams of pentose in single dose and 80 grams distributed over the whole day, laxative reaction after a larger dosage, behaviour uniform pattern of the blood pentose level, and regular excretion of this sugar in small amounts over a period of 24 hours and sometimes 36 hours after ingestion. As with the normal person, the utilization in the intestine was quantitative. The excretion of xylose in the urine also lay maximally around 20 per cent, with an average of 13.5 per cent, which is slightly lower than in normal subjects. These proportions are illustrated by a table showing the excretion diagram of 15 diabetics who received in one day 40 grams of xylose for their morning meal. (Table 2.) Repeated checks of the faeces for pentose were always negative.

Likewise, daily amounts of xylose distributed over several weeks did not result

Table 2.

15 diabetic persons of both sexes after peroral ingestion of 40 grams of xylose. Minimal 10 per cent to maximal 20 per cent are excreted, average 13.5 per cent. The pentose-concentration in the urine is at its highest after 2 to 4 hours, after which it falls progressively. After three hours the blood pentose level reaches its highest point of 60 to 80 milligram per cent and falls back to normal within the next three hours.

Pentose Excretion in g by Diabetes mellitus after intake of 40 g Xylose.															Mean pro die			
After:	Nr 1	Nr 2	Nr 3	Nr 4	Nr 5	Nr 6	Nr 7	Nr 8	Nr 9	Nr 10	Nr 11	Nr 12	Nr 13	Nr 14	Nr 15	g	%	
2 hours	3.7	1.82	0.87	0.83	1.49	1.47	1.3	1.3	0.93	1.2	1.0	1.26	1.4	1.17	1.6	1.42	3.6	
4 "	1.0	1.05	1.53	2.03	2.32	1.3	0.7	1.2	1.14	1.64	1.45	1.4	1.8	1.69	1.0	1.42	3.6	
6 "	0.16	0.66	1.18	2.05	1.28	0.65	0.73	0.7	0.5	0.66	0.85	0.7	1.3	0.7	0.4	0.83	2.1	
8 "	0.06	0.32	0.83	0.52	0.81	0.3	0.6	0.4	0.37	0.42	0.6	0.45	0.8	0.38	0.25	0.47	1.2	
10 "	0.01	0.2	0.21	0.23	0.42	0.3	0.5	0.3	0.2	0.4	0.4	0.4	0.7	0.23	0.2	0.31	0.8	
12 "	Ø	0.05	0.16	0.09	0.22	0.2	0.3	0.11	0.2	0.2	0.4	0.4	0.38	0.2	0.2	0.22	0.6	
18 "	Ø	Ø	0.37	0.15	0.39	0.3	1.0	0.1	0.25	0.2	0.84	0.5	0.85	0.18	0.5	0.43	1.1	
24 "	Ø	Ø	Ø	0.02	0.05	0.25	0.28	0.9	0.1	0.2	0.19	0.6	0.5	0.8	0.1	0.2	0.32	0.8
36 "	Ø	Ø	Ø	0.02	0.03	Ø	Ø	Ø	0.5	0.2	Ø	Ø	Ø	Ø	0.2	Ø	0.19	0.5
Total g excretion %	4.9 12.3	4.1 10.3	5.0 12.5	5.9 14.8	7.2 18.0	4.8 12.0	6.1 15.3	4.2 10.5	4.3 10.8	5.1 12.8	6.1 15.3	5.6 14.0	8.0 20.0	4.9 12.3	4.4 11.0	5.4 g = 13.5 %		

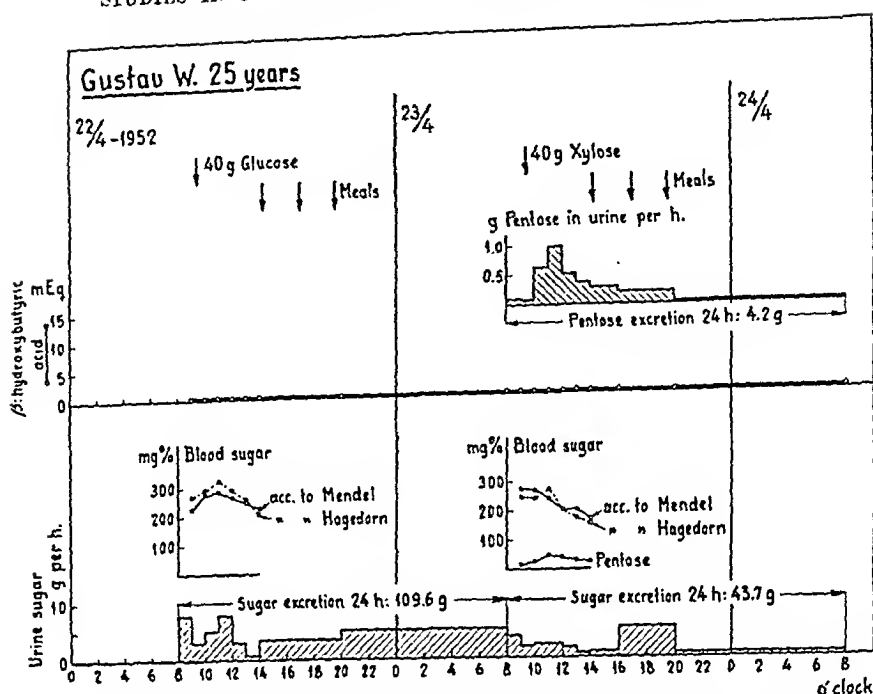
Pentose in blood mg/%

Pentose in urine g

Time (o'clock)	Pentose in blood (mg/%)	Pentose in urine (g)
2	15	1.4
4	40	1.4
5	55	0.8
6	45	0.3
8	35	0.1
10	20	0.1
12	15	0.1
14	15	0.1
16	15	0.1
18	15	0.1
20	15	0.1
22	15	0.1
24	15	0.1

in deviations from healthy subjects as regards digestibility, resorption and excretion. In no diabetic examined by us could we establish a deterioration of his state of metabolism. Moreover, glucose was never excreted in increased amounts after ingestion of xylose. The sugar balances showed nearly always a slightly lower level of glucose excretion than in the period before and after.

For further clarification of the behaviour of xylose and its influence on the intermediary metabolism of diabetics we carried out comparative glucose and xylose dosages. The comparative dosages with 40 grams of glucose and 40 grams of xylose were carried out on two consecutive days after the metabolic reaction of the patients had been established. In order to be able to follow exclusively the effects of glucose and xylose, which were administered each morning at 09.30, the patients fasted on both days until two o'clock p. m. while they were allowed liquids and stayed in bed. For the remainder of the day they were given a diet of 1,550 calories consisting of 55 grams of protein, 95 grams of fat and 110 grams of carbohydrates. Although the data collected from 12 comparative tests may be very limited, there were, nevertheless, certain observations made which may be remarkable. In nearly all patients we were able to discover a decreased glucosuria on the xylose day. On this day the excretion of glucose in the urine was on an average 40 per cent lower than on the day of the glucose test. The beta-hydroxybutyric acid values in the urine were always lowered and abbreviated on the



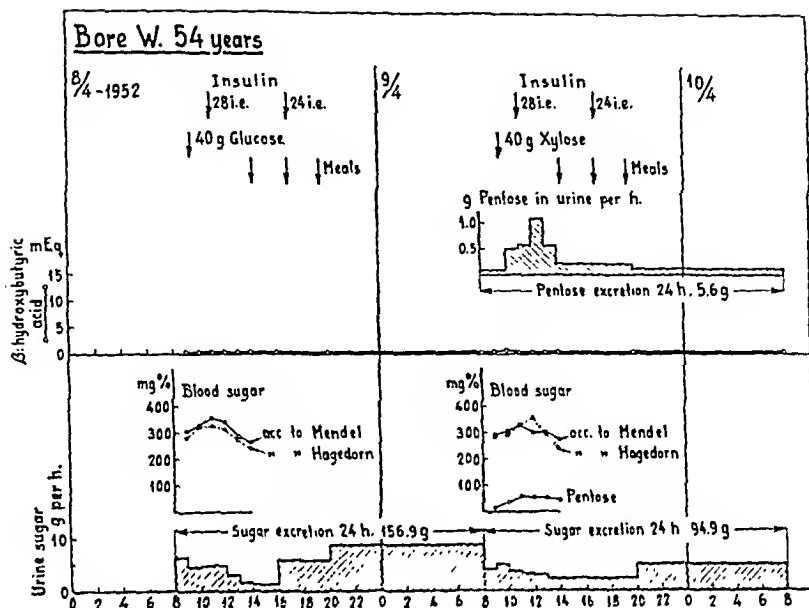
Figs. 1 to 3. Comparative loading tests with glucose and xylose, 40 grams each, made with diabetics some with acetonuria, while fasting; from 2 p. m. diet of 1,550 calories. Bed-rest, liquids allowed, and medication with insulin, equal on both days. The diagrams show lowered urine sugar values on each of the xylose days. Also decrease of the beta-hydroxybutyric acid excretion. Excretion of pentose in the urine on the xylose day about 15 per cent, pentose level in blood maximal about 60 milligrams per cent in the third hour. Similar course of the blood sugar diagrams on both days.

xylose day. The blood sugar diagrams determined by the procedure of Hagedorn-Jensen and Mendel showed no differences between the test days. All patients felt better on the day of the xylose test than on the glucose day. In the following diagrams of these tests the above described features are illustrated in detail:

It was further interesting to find that all patients who before the xylose day excreted greater amounts of glucose in the urine than on this day, a day or two later returned to the original values in their excretion of glucose.

In order to look into the question whether xylose is phosphorylated in the same way as glucose, we estimated on both test days during the fasting period the inorganic phosphate and the total-phosphate in the plasma. On both days an equally slight decrease in the inorganic phosphorus could be discovered, a fact which may point to a phosphorylation of the pentose. This question will be cleared up by further extensive examinations. The average values for inorganic phosphate in 12 diabetics decreased from 3.6 to 3.3 milligrams per cent on the glucose day and from 3.9 to 3.6 milligrams per cent on the xylose day. Dische proved the occurrence of a phosphorylation of the d-ribose contained in adenosine while esterification of inorganic phosphorus took place.

An explanation of the described test results is very difficult — above all because the catabolism of pentoses in the organism has not yet been fully cleared up. The

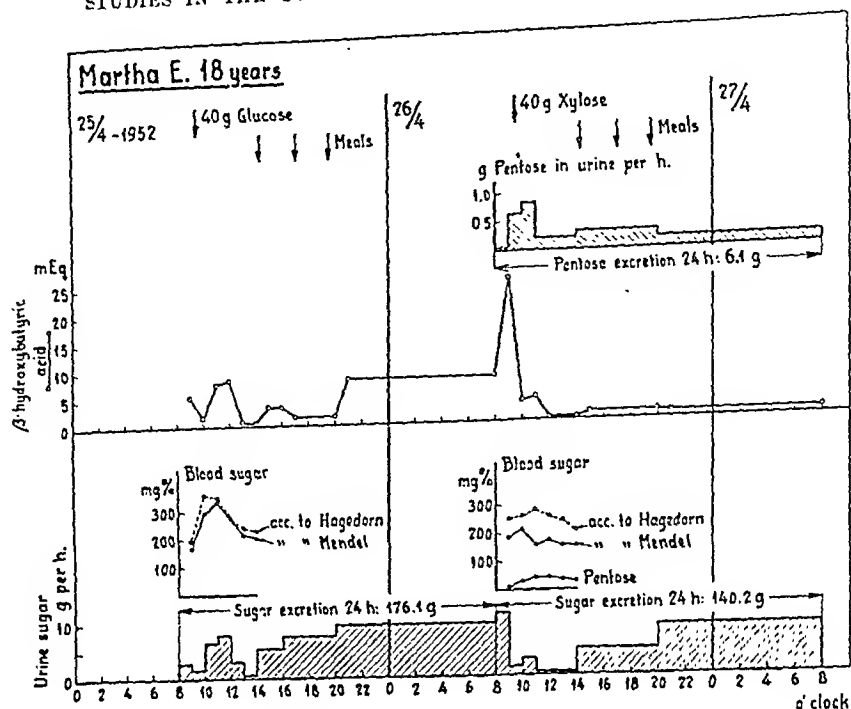


favourable influence of xylose on glucosuria and acetonuria may be attributed to a stimulating effect of this sugar on intermediary metabolism. It is possible that because of this there exists a better exploitation and utilization of the hexoses. How such a process may happen cannot yet be stated. The good effect of a vegetable diet on an impaired metabolic situation in diabetes which is explained, among other reasons, by its low carbohydrate content, possibly has something to do with this. From our investigations we may perhaps assume that a certain importance is to be attributed to the pentose or pentosan content of vegetables. According to Rubner the cell membranes of all kinds of carrots contain 23 per cent, leaf-vegetables 21 per cent and all types of fruit kinds 34 per cent of pentosans. The daily assimilation of pentosan observed in humans can attain 60 grams.

According to present-day literature the catabolism of pentose seems to resemble that of glucose. Initially phosphorylation occurs under the influence of a pentokinase. The pentose phosphate thus formed is split by aldolase, while one triose phosphate and one 2-carbon compound is formed, the latter probably being glycolaldehyde. Hereby a connection is probably formed between pentose and hexose metabolism. On the other hand it is supposed that the oxidation of pentose without previous phosphorylation is possible.

Summary.

Research on normal and 63 diabetics showed that xyloses agreed with them in every respect without any accompanying symptoms on condition that one single dosis does not exceed 40 grams and the total quantity administered does not



exceed 80 grams per day. Xylose is well resorbed and has a caloric value of 3.7 cal per gram. It may be well employed in cooking and as regards sweetness its rates between cane sugar and dextrose to which latter it is very similar in taste. Taken at an average, 15 % of the xyloses are secreted with the urine.

On the basis of the same dosis of insulin and diet, comparative experiments with 40 grams of glucosis and xyloses resulted in the following:

Favourable effect of the xyloses on the secretion of sugar in the sense of a prominent diminution as well as a favourable influence on the ketonurie.

A phosphorylation of the xyloses is assumed and documented by respective diagrams. The influence of vegetables on the diabetic's assimilation by digestion is apparently due to pentoses contained in the vegetables. The possibility of a stimulating effect of the xyloses on the assimilation by digestion with its metabolism will be revealed.

The clinical material for these examinations came partly from the Hospital of the Swedish Diabetic Foundation (Head Physician Dr. Möllerström) and the chemical analysis was performed in the Emma and B. A. Hjorth's Department of Metabolic Research in Wenner-Gren's Institute, Stockholm. I wish to express my thanks to Mrs. Eva Löfgren for excellent help in performing the analyses, and to Swedish Diabetic Foundation for financial assistance.

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The Effect of Inositol on the Rate of Phosphorus Metabolism in the Liver of Rats.

By

INGEMAR ALSTRÖM.

(Submitted for publication September 15, 1953.)

In recent years inositol has attracted great biological interest on account of the investigations made by J. G. A. Pedersen (1940) (1) into the rachitogenic properties of inositol hexaphosphoric acid in experiments with pigs, and of H. Sandstedt's (1949) (2) interesting observation that inositol has a therapeutic action in horses with polymyositis. These works were based on the fact that inositol is present in certain cereals and plants in the form of a phosphorus compound inositol hexaphosphoric acid, possibly as its CaMg salt (phytin). This in itself cannot be absorbed by the mucous membrane of the intestines. In order to be absorbed the molecule must first be enzymatically broken down by inositol phosphatase. Pedersen states that if various kinds of cereals in a finely ground state are soaked in an acid solution and kept at 40° C for 2 hours the following amounts of phosphorus combined as inositol hexaphosphoric acid will remain at the end of the experiment: wheat 0 %, rye 0 %, barley 6—31 %, oats 92 % and maize 96 %. It appears that oats do not split off phosphorus or inositol to any appreciable amount.

The above mentioned authors have put forward the hypotheses that an unbalanced diet of enzyme-deficient foods, *e. g.* oats, might cause, firstly, rachitis in pigs owing to bad absorption of the mineral element and, secondly, muscle injuries owing to bad absorption of the inositol element. Consequently, derangements in the utilization of inositol and its salt may be responsible for diseases which appear to be quite diverse in nature. These observations warrant a more thorough investigation of the nutritional properties of inositol.

Inositol has been isolated from the brain and spinal cord (3), heart muscle (4), liver (5), as well as from mammalian kidney spleen and testicles (6).

Although inositol has been demonstrated in animal tissues it has not as yet been possible to fully assess its nutritional value. Wooley (7 and 5) seems to have been the first to demonstrate the effect of inositol in experimental animals. He observed that mice reared on an inositoldeficient diet showed a characteristic loss of hair which was counteracted and prevented by inositol. Wooley proved, however, in a later investigation (8) that mice reared on an inositol-free diet developed alopecia, but in a later stage of the experiment these mice recovered. Furthermore, the amount of inositol in the tissue of mice that showed alopecia was lower than in mice that had overcome it. Moreover, the intestinal flora from mice with alopecia showed an inferior ability to form inositol in a synthetic medium in comparison with the flora from mice which has overcome alopecia. Additional support for the theory that the formation of inositol takes place in the intestinal flora has been given by Nielsen and Black (9). They observed that rats that were given sulfasuxidine in addition to their normal diet, showed alopecia and inhibited growth. The alopecia and growth inhibition were cured by the addition of inositol. The intestinal formation of inositol would in this case have been inhibited owing to the fact that sulfasuxidine checked the growth of the inositol-forming bacteria. According to Daft and Sebrell (10) the bacterial formation of inositol in rats and mice should be sufficient to cover the normal needs of these animals.

In addition to its curative effect on alopecia inositol has shown growth promoting properties in mice (Wooley), cotton rats (11), guinea pigs (12) and hamsters (13) that have been reared on a so called purified diet free from inositol. Growth in chickens (14) has also been increased when inositol was added to a synthetic diet. Inositol increased lactation in rats reared on a synthetic diet (15).

Inositol has also been tested for its effect on metabolic functions and disturbances. Weilbelhaus, Berteil and Lardy (16) observed that the addition of inositol decreased the excretion of ketone bodies in the urine in starving rats. Gavin and fellow workers (17) found that fatty degeneration of the liver caused by biotin was counteracted by inositol. Handler (18) showed that unsaturated fatty acids offset the lipotropic effect of inositol on liver rendered fatty by vitamin B deficiency. It was implied that alphasatocopherol and inositol have a synergistic effect. Dam (19) found that inositol prevented encephalomalacia and exudative diatheses in chickens reared on a vitamin E-free diet. In depancreatized dogs that received insulin Gaebler and Cissewski (20) found that inositol was one of the factors preventing glycosuria when the animals were given an overdose of sugar.

Consequently inositol seems to have not only a non-specific effect on alopecia, lactation and growth but also a more specific influence on the conditions ketonuria and fatty liver in relation to carbohydrate metabolism and also to insulin requirements.

The author's Researches.

In the present work the effect of inositol on rats has been studied with regard to the rate of growth and to phosphorus metabolism in the liver, an organ which is known to be of great general importance in carbohydrate metabolism.

Preparation: chemically pure inositol from Sheering-Karlbaum.

Experimental animals: rats of the same strain as had previously been used in studying the effect of para-aminobenzoic acid (Alström 21).

Diet: The same »semi-synthetic» and »normal» diets as used in the above-mentioned researches. The first diet was free from inositol.

Experiment I.

The rats chosen for the experiments weighed between 48 and 56 g. Only female rats were used. The experimental animals were during the first three days given the semi-synthetic diet. Thereafter half of these rats were given 200 mg inositol per 100 g of the diet. After thirty days the experiments were discontinued. The following table I shows the growth during that period, with or without the addition of inositol.

Table I.

Growth during an experimental period of 30 days with or without the addition of 200 mg of inositol to 100 g of the diet.

	Without the addition of inositol	With addition of inositol
Number of experimental animals	12	12
Average growth in g during the experimental period	69.8 \pm 2.1	70.6 \pm 1.2

Result: As shown by table I the addition of inositol under these experimental conditions did not affect the rate of growth in female rats.

Experiment II.

Altogether 40 female rats weighing between 96 and 108 g were used in the experiment. The animals were given a complete diet. Before the experiment the rats were starved for 72 hours, after which time 22 of the animals were given the complete diet with an addition of 200 mg inositol for each 100 g of diet. Two hours after they had eaten, all the animals were given intraperitoneally 5 μ e radioactive phosphorus (P_{32}) in the form of Na_2HPO_4 in an isotonic solution of glucose. The animals were killed one hour after the food had been given. The livers were removed and placed in a solution of 15 % trichloroacetic acid and carefully ground. The debris was then filtered off and washed with trichloroacetic acid until the filtrate volume was 100 cm³. A certain proportion of the filtrate was taken in order to ascertain the total phosphate and the inorganic phosphate fraction in accordance with Brigg (22) as well as to determine the number of impulses per minute, in both total phosphate and organic phosphate, by the Geiger Müller calculating apparatus. These researches were carried out at the Wenner-Gren institute, B. A. Hjorth's department for metabolic research, in accordance with their usual routine method, as described by Lindberg (23). The specific activity is the quotient between the number of impulses per minute in the phos-

phate fraction and amount of phosphate respectively. The definition relative specific activity denotes in this case the specific activity of organically bound phosphate compared with that of inorganically bound phosphate.

The relative specific activity has been calculated for each animal. The figures obtained in this way are supposed to be an expression of the rate of the phosphorus metabolic processes in the liver.

$$\text{Definitions: Specific activity} \frac{\text{Imp./min.}}{\gamma\text{P}}$$

$$\text{Relative specific activity} \frac{\text{Spec. act. for organic P}}{\text{Spec. act. for inorganic P}}$$

Table II.

Effect of addition of inositol on the rate of phosphorus metabolism in rat liver.

Inorganic phosphorus in the liver					Organic phosphorus in the liver			
	γP	Imp./min	Spec. activity	Rel. spec. activity	γP	Imp./min.	Spec. activity	Rel. spec. activity
Animals that received 200 mg inositol/100 g diet n = 22	530 ± 24.4	88,617 $\pm 7,771$	170 ± 14.5	100	1,545 ± 146.7	90,663 $\pm 7,301$	64.8 ± 6.5	39.1 ± 2.9
Control animals n = 18	592 ± 41.3	124,700 $\pm 15,375$	213 ± 26.2	100	1,514 ± 230.1	166,000 $\pm 7,270$	118 ± 14.5	58.2 ± 7.5
Difference control animals — inositol-treated animals	$t = 1.307^1$	$t = 2.087^1$	$t = 1.421$		$t = 0.136$	$t = 8.394^2$	$t = 3.307^2$	$t = 4.113^2$

n = number of animals.

¹ Probability that difference due to chance < 0.05 but > 0.01 .

² " " " " " " " < 0.01 " > 0.001 .

³ " " " " " " " < 0.001

Result: From table II it can be seen that the amount of phosphorus in the liver, whether inorganically or organically bound, is not influenced by the addition of inositol. On the other hand the number of impulses per minute, determined in the Geiger Müller counter, in the entire liver was considerably lower in rats that had received inositol than in the control animals with regard to both inorganically and organically bound phosphorus. This produced a statistically definite (the probability of chance difference < 0.001) decrease in the relative specific activity. This may be interpreted as signifying that the rate of phosphorus metabolism in the liver had decreased under the influence of inositol.

Discussion.

The researches were carried out in order to ascertain the effect of inositol on experimental animals. The classical method, depriving the animals of the substance, the effect of which is to be examined, and then studying the effect of an addition of the same substance on the deficient animals, was tried out on rats. With regard to inositol one can conclude that the bacterial flora can form inositol and also that this substance can be absorbed with the diet, *i. e.* after being formed from inositol hexaphosphoric acid. This twofold supply seems well suited to prevent the occurrence of an inositol deficiency, which may explain the fact that no further growth promoting effect of inositol was noticed during my experiments with an inositol-free diet.

If the rats were starved and given the same amount of inositol added to a complete diet a rapid effect of the inositol addition could be noticed with the radio-active phosphorus isotope P_{32} as an indicator. The inositol decreased the rate of phosphorus metabolism in the liver three hours after the feeding. These investigations have also shown that free inositol influences the rate of phosphorus metabolism when given in considerably smaller amounts than the intake of this vitamin when present in natural diet (compare Burkholder 24). To the previously described properties of inositol in animal researches another one can consequently be added, namely that inositol when given to previously starved rats decreases the rate of phosphorus metabolism in the liver.

The effect of inositol corresponds to that of paraaminobenzoic acid on the rate of phosphorus metabolism in the liver shown in experiments carried out in the same way (Alström 21).

Summary.

With a dose of 200 mg inositol/100 g semi-synthetic inositol-free diet, no growth promoting effect was obtained in experiments with female rats. This result has been taken to indicate that the inositol supply was adequate without further addition, probably owing to the formation of inositol by the bacterial flora. The same dose of inositol given to rats that had been starved and afterwards offered an inositol-supplemented adequate diet, led to a decrease in the rate of phosphorus metabolism in the liver, measured by the radioactive phosphorus isotope P_{32} .

References.

1. Pedersen, J. G. A.: Experimentell Rachitis hos svin. Disp. Köpenhamn 1940. —
2. Sandstedt, H.: Nordisk Veterinärmedicin. 424, 5. 1949. —
3. Folch, J. and Woolley, D. W.: J. Biol. Chem. 142: 963, 1942. —
4. Winter, L. B.: Biol. Chem. J. 28: 6, 1934. —
5. Woolley, D. W.: J. Biol. Chem. 139: 29, 1941. —
6. Hawk, P. B., Oser, B. L. and Summerson, W. H.: Practical Physiological Chemistry 12th Ed. 1947. —
7. Woolley, D. W.: Science 92: 384,

1940. — 8. Woolley, D. W.: *J. Exptl. Med.* 75: 277, 1942. — 9. Nielsen, E. and Blæk, H.: *Proc. Soc. Exptl. Biol. Med.* 55: 14, 1944. — 10. Daft, S. and Sebrell, W. H.: *Vitamins and Hormones* III: 49, 1945. — 11. McIntire, J. M., Schweigert, B. S. and Elvehjelm, C. A.: *J. Nutrition*, 27: 1, 1944. — 12. Hagan, A. G. and Hamilton, J. W.: *J. Nutrition* 23: 533, 1942. — 13. Coperman, J. M., Weisman, H. A. and Elvehjelm, C. A.: *Proc. Soc. Exp. Biol. and Med.* 52: 250, 1942. — 14. Hegsted, D. M., Briggs, G. M., Milk, R. C., Elvehjelm, C. A. and Hart, E. B.: *Proc. Soc. Exp. Biol. Med.* 47: 376, 1942. — 15. Sure, B.: *Nutrition* 26: 275, 1943. — 16. Wiebelhaus, V. D., Bethel, J. and Lardy, H. H.: *Arch. Biochem.* 13, 1947. — 17. Gavin, G., Patterson, J. M. and McHenry, E. W.: *J. Biol. Chem.* 148: 275, 1943. — 18. Handler, P.: *J. Biol. Chem.* 162: 77, 1946. — 19. Dam, H.: *J. Nutrition* 27: 193, 1944. — 20. Gaebler, O. H. and Cissewski, W. E.: *Endocrinology* 36: 227, 1945. — 21. Alström, I.: Inverkan av sulfanilamid och dess antagonist Paraaminobenzoesyra på den djuriska organismen huvudsakligen med hänsyn till kolhydratomsättningen. *Diss. Suppl. till band 4, Skand. Vet. Tidskr.* 1948. — 22. Brigg: *J. Biol. Chem.* 53: 13, 1922. — 23. Lindberg, O.: On the occurrence of Propanediol Phosphate and its Effect on the Carbohydrate Metabolism in Animal Tissues. *Diss. Arkiv för Kemi, Mineralogi och Geologi. Band 23 A. nr. 2.* — 24. Burkholder, P. R.: *Science*, N. S. 97: 1943.
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Effect of the Digitalis Glucoside Digitoxin on the Phosphorus Metabolism in Heart and Liver of Rats, Measured by the Radioactive Phosphorusisotope P_{32} .

By

INGEMAR ALSTRÖM.

(Submitted for publication September 15, 1953.)

Digitoxin appears to be the digitalis preparations which at present attracts the greatest interest on account of its pharmacodynamic properties.

By hydrolyses of digitoxin, digitoxigenin is formed together with digitoxose, a sugar-like substance.

Digitoxigenin is a steroid chemically related to biologically active sex hormones and vitamin D. This and the fact that digitoxin is effective in very small concentrations make its action comparable to the influence of a hormone or vitamin on the heart.

The question then arises whether digitoxin affects the function of organs other than the heart and, if so, what biochemical processes this involves. Earlier investigations inform us of the effect of digitalis preparations on carbohydrate metabolism.

Haendel & Munilla (1) demonstrated that the content of glycogen in the liver and skeletal muscles in dogs treated with a digitalis preparation, »Digalen», was not affected, whilst the content of glycogen in the heart muscles decreased. The concentration of digitoxin in the digitalis preparation used was not known.

Lasch and Friege (2) found that the total amount of carbohydrate in the liver and heart increased during treatment with digitalis. Liebig (3) found that 0,2 g digitalis in the form of »digalen» and digipurat caused an increased level of blood sugar in rabbits and also resulted in a decrease of the amount of glycogen in the heart and muscles, particularly in the latter.

Liebig discusses the possibility that the carbohydrate in the muscles is mobilised under the influence of digitalis to the advantage of the increased needs of the

heart. The reserve of glycogen in the liver is also decreased under the influence of digitalis. The decrease in the content of glycogen in the liver was, however, as Liebig states, difficult to establish on account of the great variations, probably due to the fact that he had not taken into account the normal 24-hourly cycle of variations in the liver glycogen content.

Bomskov and associates (4) have shown that digitalis derivatives affect the basal metabolism in guinea pigs. Small doses of digitalis counteracted the increase in metabolism that was caused by thyrotropic hormone, whilst big doses had the same effect as thyrotropic hormone.

It can consequently be seen from these accounts that digitalis appears to affect carbohydrate metabolism not only in the heart but also in the muscles and liver, as well as influencing the basal metabolism.

My Own Researches.

In this work I have investigated whether digitoxin has any effect on the liver and heart with regard to the rate of phosphorus metabolism, using the radioactive phosphorus isotope P_{32} . The importance of phosphorus metabolism for carbohydrate metabolism is well known and is not discussed in this paper. For these experiments male rats weighing 100 g were used. Firstly the minimum toxic dose was ascertained. In order to do this varying doses of digitoxin were given intraperitoneally to a series of rats that had previously been starved for a certain time and then been offered unlimited food. Following a dose of 0,1 mg digitoxin injected intraperitoneally signs of toxic symptoms were observed. 1/3 of this dose, 0,033 mg, did not during my experiments produce any toxic symptoms whatsoever. Both these doses were used in the following experiments.

Procedure: In accordance with the experimental procedure adopted by Alström (5) for isotope experiments, the rats were starved for a period of 72 hours after which time they were allowed to eat ad lib. Two hours after they received food they were given intraperitoneally 0,033 or 0,1 mg of digitoxin (digitrin Astra) with 5 μ c radioactive phosphorus P_{32} in the form of Na_2HPO_4 in an isotonic solution of glucose. Control animals were also used in the experiments. These were treated in the same manner and received radioactive phosphorus (but not digitoxin). The rats were killed by decapitation one hour after injection. With this method all the experimental animals were in the same stage of food absorption at this juncture. The liver and the heart were removed and placed in a solution of trichloroacetic acid. Afterwards these separate organs were very carefully ground. The debris was filtered off and washed until the filtrate volumes had attained 100 and 50 cc respectively. A measured portion of this filtrate was taken in order to ascertain the total phosphate and the inorganic phosphate in accordance with Brigg (6), as well as the distribution of the radioactive phosphorus through determining the number of impulses per minute, in both total phosphate and inorganic phosphate, in the Geiger-Müller counter in accordance with the method described by Lindberg (7). From the figures thus obtained there were determined the amount of organic

EFFECT OF THE DIGITALIS GLUCOSIDE DIGITOXIN.

Table I.

Effect of non-toxic dose (0.033 mg) of digitoxin on

	Inorganic phosphorus				Organic phosphorus			
	γ P	Imp./min.	Spec. act.	Rel. spec. act.	γ P	Imp./min.	Spec. act.	Rel. spec. act.
A. heart								
Digitoxin treated animals	139.2	10 393	73.9	100	245.5	6 183	28.6	41.3
Number of experimental animals 15	± 8.75	$\pm 1 469$	± 9.19	± 34.19	± 34.19	± 890	± 4.08	± 5.0
Control animals	141.4	11 200	81.2	100	267.7	3 551	16.6	21.7
Number of experimental animals 17	± 8.79	$\pm 1 316$	± 10.21	± 35.90	± 542	± 2.85	± 2.92	
Difference between digitoxin-treated animals — control animals	$t = 0.173$	$t = 0.410$	$t = 0.559$	$t = 0.446$	$t = 2.526$	$t = 2.423$	$t = 3.11$	
B. liver								
Digitoxin treated animals	732.8	167 413	228.9	100	1623.7	134 520	85.8	39.2
Number of experimental animals 15	± 32.92	$\pm 9 185$	± 14.33	$\pm (0)$	± 185.05	$\pm 14 779$	± 6.90	± 3.66
Control animals	653.9	136 924	197.4	100	1 695.2	121 291	78.6	40.6
Number of experimental animals 17	± 79.8	$\pm 12 349$	± 20.40	$\pm (0)$	± 137.64	$\pm 12 059$	± 9.80	± 4.15
Difference between digitoxin-treated animals — control animals	$t = 0.913$	$t = 1.931$	$t = 1.267$	$t = 0.310$	$t = 0.694$	$t = 0.602$	$t = 0.24$	

¹ probability that difference due to chance < 0.05 but > 0.01
² probability that difference due to chance < 0.01

phosphate and the number of impulses per minute in the organic fraction of phosphorus and the relative specific activity.

Definitions: Specific activity = $\frac{\text{Impulses/min.}}{\gamma \text{ P}}$

Relative specific activity = $\frac{\text{spec. activity of org. P}}{\text{spec. activity of inorg. P}}$

The subtoxic doses produced the following effect. In the organic fraction of phosphorus in the heart the numbers of impulses per minute probably increased significantly. This increase was accompanied by a statistically definite increase in the specific activity of the organic phosphorus fraction as well as in increased relative specific activity. This treatment with digitoxin produced no statistically proved effect in the liver.

The toxic dose of digitoxin produced no effect on the heart, but a statistically probable decrease in the specific activity of the organic fraction of phosphorus in the liver, which was accompanied by a statistically definite decrease in the relative specific activity in the liver.

Discussion. The finding that the digitalis glycoside digitoxin affects carbohydrate metabolism in heart and other organs in different ways corresponds with the results of older experiments with different digitalis preparations (1, 3). The differ-

Table II.

Effect of toxic dose (0.1 mg) of digitoxin on

	Inorganic phosphorus				Organic phosphorus			
	γ P	Imp./min.	Spec. act.	Rel. spec. act.	γ P	Imp./min.	Spec. act.	Rel. spec. act.
<i>A. heart</i>								
Digitoxin treated animals	141.8	12 360	90.8	100	234.0	6 136	22.9	22.8
Number of experimental animals 14	± 8.0	$\pm 2\ 081$	± 16.7		± 28.2	$\pm 2\ 029$	± 5.34	± 2.76
Control animals	125.1	12 396	116.9	100	173.7	5 735	32.2	21.9
Number of experimental animals 14	± 9.4	$\pm 2\ 352$	± 26.7		± 32.8	$\pm 1\ 828$	± 10.3	± 3.0
Difference between digitoxin-treated animals — control animals	$t = 1.352$	$t = 0.011$	$t = 0.830$		$t = 1.394$	$t = 0.142$	$t = 0.816$	$t = 0.20$
<i>B. liver.</i>								
Digitoxin treated animals.	1 024.9	189 886	198.0	100	2 238.4	165 500	40.0	35.3
Number of experimental animals 14	± 62.1	$\pm 47\ 933$	± 50.6	$\pm (0)$	± 153.6	$\pm 35\ 730$	± 6.39	± 1.93
Control animals	945.6	164 871	212.2	100	2 318.3	222 293	97.6	44.8
Number of experimental animals 14	± 74.0	$\pm 36\ 473$	± 52.9	$\pm (0)$	± 238.5	$\pm 61\ 411$	± 25.7	± 1.69
Difference between digitoxin-treated animals — control animals	$t = 0.821$	$t = 0.415$	$t = 0.194$		$t = 0.801$	$t = 0.280$	$t = 2.177$	$t = 3.603$

¹ probability that difference due to chance < 0.05 but > 0.01² probability that difference due to chance < 0.01 but > 0.001

ences in effect between small and large doses have also been observed earlier (4). The new finding in my experiments is that the heart is affected only by small non toxic doses of the pure digitalis glycoside digitoxin and that toxic doses do not affect the heart but decrease the turnover rate of phosphorus in the liver. The turnover rate of phosphorus in the liver on the other hand was not affected with small (therapeutic) doses. With help of radioactive phosphorus it will be possible to determine the limits for the therapeutic and toxic doses of digitalis.

Summary.

The rate of phosphorus metabolism in the heart and liver of rats treated with subtoxic doses of digitoxin has been examined with the help of the radioactive phosphorus isotope P_{32} . Subtoxic doses increased the rate of phosphorus metabolism in the heart but left the liver unaffected. Toxic doses left the heart unaffected but decreased the rate of phosphorus metabolism in the liver.

The enhancing effect of small doses of digitalis on the rate of phosphorus metabolism in the heart might be a concomitant of, or be the basis for, the therapeutical effect of digitalis, whilst the suppressing effect of toxic doses of digitalis on the rate of phosphorus metabolism in the liver might be a concomitant of, or be the basis

for, the toxic action of digitalis. It is of great interest to note that the toxic dose leaves the heart unaffected, an observation that should not lack practical importance.

References.

1. Haendel, E. and Munilla, H.: Biochem. Z: 212. 35, 1929. — 2. Lasch, E. and Frieger, S.: Z. exper. Med. 88: 588, 1933. — 3. Liebig, H.: Archiv für Experimentelle Pathologie und Pharmakologie 137, 1940. — 4. Bomskov, Ch., Kaulla, K. and Maurath, J.: Archiv für Experimentelle Pathologie und Pharmakologie 198: 213, 1941. — 5. Alström, I.: Inverkan av sulfanilamid och dess antagonist para-aminobenzoesyra på den djuriska organismen huvudsakligen med hänsyn till kolhydratomsättningen: Skand. vet. Tidskr. suppl. till band 4, 1948. — 6. Brigg, J.: Biol. Chem. 53: 13, 1922. — 6. Lindberg, O.: Arkiv för Kemi, Mineralogi och Geologi 23 A 2 Diss. 1946.
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Studies of the Renal Plasma Flow.

By

HELGE LAAKE.

(Submitted for publication October 22, 1953.)

Introduction.

Para-amino-hippuric acid has replaced diodrast (D) more and more both for the clinical diagnosis of renal function and for physiological studies of the kidneys. Recent investigations have, however, shown that, with low plasma concentrations, the clearance (Cl) figures are identical for these substances. With regard to D it has been repeatedly shown that, with falling plasma concentrations (P_D) during successive periods, there is a fall of the Cl figures. Various writers have interpreted their observations in the most widely different ways. Brun and his associates (1949) maintain that the difference in the arterio-venous concentration for D is the responsible factor, whereas Hogeman (1948) concludes that the most likely explanation is to be found in the varying protein-fixation of D. In French quarters (quoted by Hågensen and his associates) the assumption is made that an «inertie tubulaire» exists, with low plasma concentrations. But this assumption is not confirmed by the investigations by Hågensen and his associates (1951). Handley and his associates (1949) refer to the significance of the part played by dehydration for the renal plasma flow. Lastly, the D diffusion from erythrocytes to plasma during intrarenal circulation has also been discussed as a causal factor.

At the Medical Department B. of the Rikshospital, we have observed in the course of our studies of renal function a simultaneous reduction of inulin clearance (Cl_i) and Cl_D in successive periods. We came therefore to ask whether the reduced glomerular filtration is of significance with regard to the reduction of Cl_D , or whether the factors determining the reduction of Cl_i in successive periods (Laake, Acta Med. Scand. in the press) also influence the Cl_D figures. In order, if possible, to throw light on this problem, we have undertaken the simultaneous recording of Cl_i in patients whose renal function was presumably normal.

Procedure.

The procedure adopted for the determination of Cl_I was the same as that described earlier at this hospital. Thirty minutes before the Cl periods were started, 20–25 mg of diodrast-I per kg body weight were given by intravenous injection. The injection of diodrast must be given slowly, as a temporary depression of Cl_D may otherwise occur (Landowne and his associates, 1947). The analyses of diodrast-I in plasma and urine were undertaken in a way described earlier by the author (Laake, 1945). The mean P_D in the Cl periods is practically identical whether the arithmetic, logarithmic, or planimetric mean be employed. In our own calculations we have employed the logarithmic mean. In 15 patients, P_D was examined after a single intravenous D injection, and like other observers we found a linear fall of P_D from 15 to 20 minutes after the injection.

Own Investigations.

Nine patients with healthy kidneys (6 women and 3 men), all under the age of 30, underwent 12 Cl tests (see table I), each including 5 successive periods. Irrespective of the period, the mean (corrected to 1.73 m² body surface) figure is:

$$Cl_D 452 \pm 66.7 \text{ ml/min.}$$

Table I.

Inulin and diodrast clearance after a single intravenous injection of these substances.

Normal material.

Pas. nr.	Period	Cl_I ml/min.	Diodrast-I mg/100 ml plasma	Cl_D ml/min.
1	1	136.5	2.9	518.0
	2	127.7	1.8	450.0
	3	123.5	1.1	570.0
	4	100.9	0.8	410.0
	5	96.0	0.6	435.0
1	1	147.2	2.6	559.0
	2	150.0	1.9	390.0
	3	133.6	1.3	485.0
	4	115.7	0.95	405.0
	5	103.9	0.70	430.0
2	1	116.7	2.55	535.0
	2	123.5	2.1	585.0
	3	109.0	1.5	420.0
	4	92.3	1.05	380.0
	5	83.9	0.85	450.0
2	1	117.4	3.3	490.0
	2	116.8	2.65	547.0
	3	107.6	1.95	465.0
	4	93.3	1.30	405.0
	5	94.8	0.90	390.0

Pas. nr.	Period	Cl _r ml/min.	Diodrast-I mg/100 ml plasma	Cl _D ml/min.
3	1	152.3	3.65	648.0
	2	136.7	2.55	505.0
	3	144.3	2.05	550.0
	4	125.6	1.4	420.0
	5	102.5	1.0	460.0
4	1	111.6	2.45	542.0
	2	109.0	1.80	430.0
	3	101.6	1.25	500.0
	4	83.7	0.90	470.0
	5	75.3	0.75	510.0
5	1	118.9	3.75	491.0
	2	123.7	2.25	530.0
	3	112.3	1.70	390.0
	4	92.6	1.20	455.0
	5	99.3	0.95	395.0
5	1	116.6	2.95	420.0
	2	109.3	2.30	490.0
	3	114.8	1.90	385.0
	4	99.6	1.35	465.0
	5	87.3	1.10	390.0
6	1	112.3	3.15	459.0
	2	110.6	2.25	520.0
	3	102.9	1.75	410.0
	4	89.2	1.30	375.0
	5	73.1	0.85	400.0
7	1	119.4	1.95	505.0
	2	123.5	1.55	530.0
	3	117.7	1.30	445.0
	4	102.4	1.05	375.0
	5	92.1	0.80	360.0
8	1	145.0	3.95	390.0
	2	126.9	3.00	435.0
	3	130.6	2.15	400.0
	4	114.3	1.70	320.0
	5	99.8	1.30	355.0
9	1	150.9	2.30	438.0
	2	143.6	1.95	468.0
	3	139.3	1.45	395.0
	4	128.7	1.10	420.0
	5	119.3	0.85	370.0

This is a somewhat higher figure than Hilden (1943) obtained with his procedure. Working with a procedure similar to that adopted for our Cl_D investigations, Foà and Foà (1942) found 556 ml/min., *i.e.* practically the same figure as that recorded with the other methods of administering D. But these observers did not correct for »delay time», and this omission explains their high mean figures. The mean Cl_D figures for each period by itself are given in table II. The regression line for Cl_D period means (see fig. I) is straight,

$$\text{est. Cl}_D = 529 - 25.7 t,$$

Table II.
Period means for diodrast clearance (Cl_D).

	Periods				
	1	2	3	4	5
Cl_D ml/min.	500	490	451	408	412

and the regression coefficient — 25.7 is significantly different from 0 at the 1 % level. One-way and two-way classifications were made with variance analysis which also enabled us to test the variations in Cl_D in the different persons tested. We now found that the difference between Cl_D in the first and the third periods

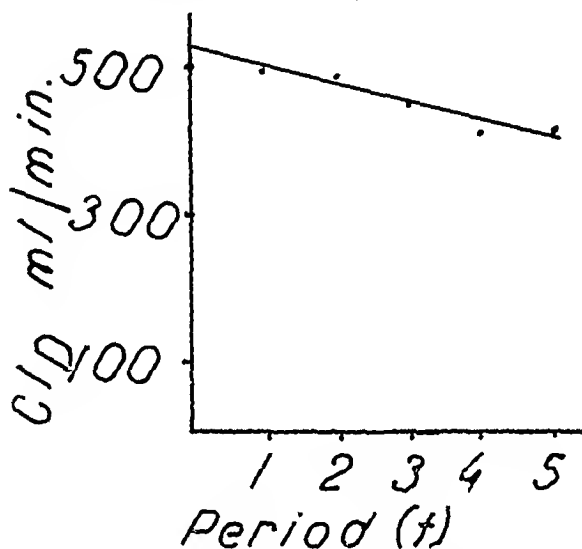


Fig. I. The regression line for Cl_D period means.

was statistically significant at the 5 % level, but at the 1 % level there was a significant difference only between the first and the fourth periods. *These studies show that a simultaneous reduction of Cl_I and Cl_D occurs in successive periods.* By comparing the slant of the regression lines for Cl_I and Cl_D , expressed by the regression coefficient, we can obtain a measure of the degree of reduction of the glomerular filtration and the renal plasma flow. Both series of observations (Cl_I and Cl_D) are readjusted by calculation in such a way that they show the same standard deviation, — *i. e.* 1. The regression coefficient (r) between Cl figure and the period (t) becomes in the case of inulin:

$$r_I = \div 0.622$$

and in the case of diodrast:

$$r_D = \div 0.617.$$

In other words, Cl_I and Cl_D have practically the same correlation with t in this material; *the reduction of Cl_I and Cl_D from period to period is almost of the same size.*

This conclusion is further confirmed by calculating the filtration fraction (FF). In this material (see fig. II) the FF mean was 25.6 %, and the standard deviation 4.8 %. In other words, a somewhat higher FF figure than is to be found on a permanent supply of D.

Davies and Shock (1950) have analysed the variability of Cl_D from day to day and from period to period on the same day. They found that the variations from one day to another were greater than the period variations on the same day. They

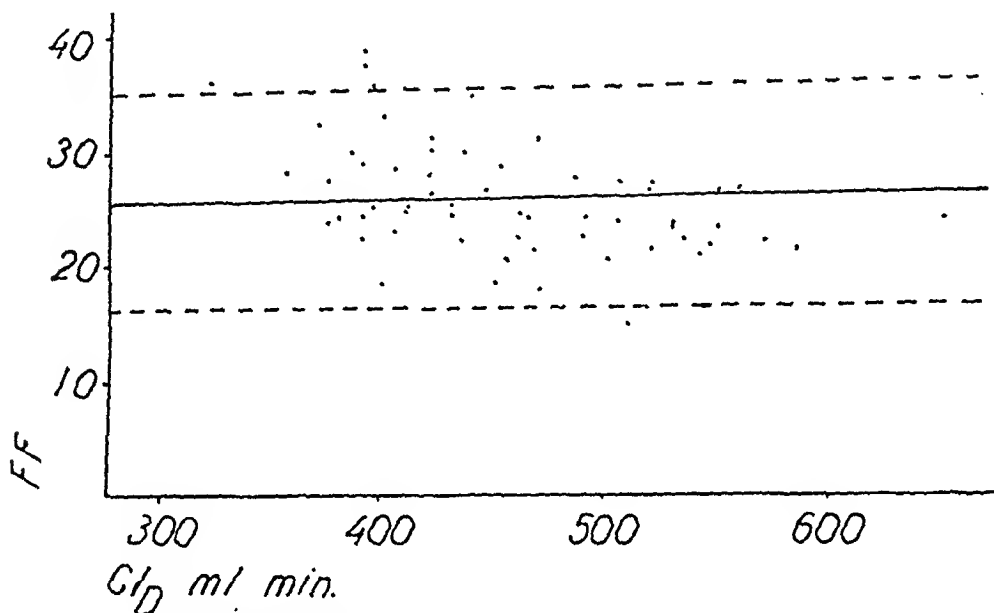


Fig. II. The filtration fractions (FF in %) for all the observations.

noticed that, with the same person tested, the deviations for Cl_D in successive periods grouped themselves about 33 ml/min./1.73 m² body surface. By calculating the confidence area for Cl_D in our material, we found at a confidence degree of 99 % and 95 % respectively, Cl_D means of 452 ± 22.9 ml/min. and 452 ± 17.2 ml/min. In 5 % of the Cl tests we carry out, the mean of n observations will fall outside the area $500 \pm \frac{113}{\sqrt{n}}$ ml/min. for 1. period. Our findings coincide very well with those of Davies and Shock, of course confirming their observations with regard to the variability of Cl_D .

When we calculate the regression for each Cl test in this material, we fail to find evidence of any definite P_D reduction of the Cl figures. This also shows that the course of the regression line for all the observations runs straight.

Discussion.

In the clinical investigations recorded here, the extraction ratio (Excr.) for D is not determined, and the Cl_D figures are not corrected. Excr._D is relatively con-

stant (Josephson and associates 1950), an increasing age does not lead to significant changes (Davies and Shock). We are not, however, justified in calculating the total renal plasma flow on the basis of the mean Excr._D .

Simultaneous Cl investigations may entail the administration of test substances for the determination of a single function, and this may interfere with the determination of another function. White and his associates (1940) found almost identical Cl_D figures in a normal material when the renal plasma flow was partly determined by itself and partly in connexion with Cl_I . These findings are confirmed by our own observations. There is no deposit of D in the tubules, and it is also unlikely that synthesis of this substance occurs.

When the test conditions are constant, the renal plasma flow under normal conditions is fairly unchangeable, and when findings are repeated in the same person over a period of 4 months, the variations are not more than $\pm 15\%$ (Smith, 1943). Even if, by an effective arrangement of the tests, we try to reduce the significance of the emotional factors as much as possible, we cannot prevent the possibility of repeated Cl tests eliciting a pressor phase with reduction of the renal plasma flow.

An analysis of the FF figures can to a certain extent present a picture of the functional condition of the arterioles of the kidneys. By variance analysis of the FF figures, we were not able in our series of tests to demonstrate statistically significant differences from one period to another either with one-way or two-way classification. This points against the conclusion that functional changes in the blood supply of the glomerular apparatus during the test periods could be a causal factor in the reduction of the Cl figures.

It would seem that the Cl figures are influenced by the mode of administration of D. The Cl_D figures are approximately identical whether D is given by continuous intravenous, subcutaneous or intramuscular injection. The reduction of Cl_D in successive periods after a single intravenous injection is interpreted by certain writers as a result of the rapid P_D fall, supposed in their opinion to render the arterial D concentration lower than the peripheral venous D concentration. Conversely, with a rising P_D the arterial D concentration should be higher than the venous D concentration. Brun and his associates (1949) maintain that the Cl_D figures become correct when arterial D concentration is employed instead of the venous in the Cl formula. In so far as iodine is concerned (Robson and associates, 1950) equilibrium is established between plasma and extracellular fluid during the Cl periods. Newman and his associates (1949) have, however, shown that Cl_D was constant with P_D rising from 2.18 to 8.3 mg/100 ml. This should be an argument against the significance attached to the gradient of the arterio-venous concentration for the fluctuations of Cl figures in successive periods. With the procedure we have followed, P_D falls slowly during the periods (see table I), and this explains our relatively high means for Cl_D . Studies of the course of the regression line for the Cl periods tend to refute the assumption that the changes in P_D are a central causal factor responsible for the reduction of Cl_D during the periods. Confidence area studies also confirm the belief that the P_D fall cannot be of essential importance to the Cl_D reduction in our material. The erythrocytes' D transport does not in-

fluence the Cl figures as the amount of D which diffuses from the blood corpuscles during the renal passage is minimal (Smith and his associates, 1945). The dissociation constant for D is of no significance to the tubular excretion of this substance. Investigations of protein fixation of diodrast-I (Smith and Smith, 1938) show that in the concentration area 5.0 to 0.6 mg/100 ml there is a variation of the free fraction between 77.5 and 73 %. It appears from Hegeman's dialysis tests (1948), that a relatively greater fraction of diodrast-I is fixed when there is a low P_p . The varying protein fixation may influence the D diffusion within the capillaries, but in practice this factor is of no importance to Cl_p (Smith, 1941). Experiments on animals have shown that the degree of hydration is of no importance to Cl_p (Dicker and Heller, 1945) and variations of diuresis do not influence the Cl figures. The lymphatic renal drainage may also conceivably contribute to the reduction of the Cl figures, but comparative investigations of the glomerular and tubular circulation of the blood of human beings with healthy kidneys (Cargill, 1949) show that these figures are identical. This suggests that the lymphatic drainage plays no important part in this respect.

Diodrast is mainly excreted by the tubules, but some of it is filtered in the glomeruli, this latter fraction being a product of the free P_p and Cl_f . Throughout the Cl periods there is a real reduction of the glomerular filtration, and this may influence the total D excretion and consequently also Cl_p . We have tried to throw light on the numerical importance of the Cl_f reduction for the Cl_p figures by correcting Cl_p for the reduced glomerular filtration of D throughout the periods. Such a calculation is apt to be faulty, and it is particularly the varying protein fixation of D -iodine which is of importance as a source of error, obliging us to accept our findings with some reserve. These calculations seem to show that the reduced glomerular iodine filtration throughout the periods is not so great that it influences the Cl_p figures.

Every factor which reduces the circulation of interstitial fluid in the kidneys reduces the transport of a test substance to the excretory tissues, entailing lower Cl figures. In this respect an increased intrarenal pressure is a factor of importance. Investigations of Cl_f at our hospital indicate that the increased intrarenal pressure which arises during water diuresis is one of the causes of the reduction of the Cl figures during successive periods. It is tempting to assume that the simultaneous reductions of Cl_f and Cl_p may be due to the same cause, *i. e.* an increased intrarenal pressure.

Summary and Conclusions.

The renal plasma flow (Cl_p) was investigated after a single intravenous injection of diodrast. Tables I and II show that Cl_p falls in successive periods, and variance analysis shows that the differences in the mean figures are statistically significant from the third period. There was a simultaneous reduction of inulin clearance (Cl_f) and Cl_p , and when the regression lines for Cl_p and Cl_f were compared, it was found that the reduction of the clearance figures was almost of the same degree. An analysis of the filtration fraction figures suggests that there are no functional

changes in the blood supply of the glomerular apparatus during the test periods acting as the cause of the reduction of the clearance figures.

With the procedure adopted in the present study, it was found that the concentrations of diodrast in the plasma fell slowly. Studies of the course run by the regression line during the clearance periods and the confidence areas suggest that the fall of the diodrast plasma concentration during the periods can have had no influence of importance to the reduction of Cl_D .

The glomerular filtration of diodrast-iodine was reduced during the clearance periods, but this reduction was not so great that it influenced the Cl_D figures.

Our studies of the renal plasma flow, and investigations at our hospital of Cl_D published earlier indicate that, with the procedure we have employed, the increased intrarenal pressure during water diuresis is the essential factor which contributes to the reduction of the clearance figures in successive periods.

References.

- Brun, C., Hilden, T. and Raaschou, T.: *J. clin. invest.* 28, 1949, 144. — Cargill, W. H.: *J. clin. invest.* 28, 1949, 533. — Davies, D. F. and Shock, N. W.: *J. clin. invest.* 29, 1950, 491 and 496. — Dicker, S. E. and Heller, H.: *J. physiol.* 103, 1945, 449. — Foà, P. P. and Foà, N. L.: *Proc. Soc. exper. Med. a. Biol.* 51, 1942, 375. — Handley, C. A., Sigafos, R. B. and Forge, M.: *Amer. J. Physiol.* 159, 1949, 175. — Hilden, T.: *Ugeskr. for Læger* 105, 1943, 863. — Hogeman, O.: *Acta Med. Scand. suppl.* 216, 1948. — Hågensen, N. R., Keiding, R. and Bischoff, K.: *Scand. J. clin. a. lab. invest.* 3, 1951, 92. — Josephson, B., Werkö, L. and Bucht, H.: *Scand. J. clin. a. lab. invest.* 2, 1950, 149. — Landowne, M. and Alving, S.: *J. lab. a. clin. Med.* 32, 1947, 931. — Laake, H.: *Acta Med. Scand. suppl.* 168, 1945. — Newman, E., Kattus, E., Genecin, A., Genest, J., Calkins, E. and Murphy, J.: *Bull. Johns Hopk. Hosp.* 84, 1949, 135. — Robson, J. S., Ferguson, M. H., Olbrich, O. and Stewart, C. P.: *Quart. J. exper. Physiol.* 35, 1950, 173. — Smith, H. W.: *J. clin. invest.* 20, 1941, 631. — Smith, H. W.: *Lectures on the kidney*, Kansas 1943. — Smith, H. W.: *The Kidney*, New York 1951. — Smith, H. W., Finkelstein, N., Aliminos, L., Crawford, B. and Graber, M.: *J. clin. invest.* 24, 1945, 388. — Smith, W. W. and Smith, H. W.: *J. biol. Chem.* 124, 1938, 107. — White, H. L., Findley, Th. jr. and Edwards, J. C.: *Proc. Soc. exper. Biol. a. Med.* 43, 1940, 11.
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Local Haemorrhage and Necrosis of the Skin and Under-lying Tissues, During Anti-Coagulant Therapy with Dicumarol or Dicumacyl.

By

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(Submitted for publication October 20, 1953.)

Introduction and General Remarks.

The extensive application of anti-coagulants of the dicumarol-group has shown up to date only one serious complication, the haemorrhage due to deficiency of plasma-prothrombin. The different localisations of the haemorrhages explain fully the different clinical pictures ensuing from them. As soon as the plasma-prothrombin concentration increases, the haemorrhages subside. When the bleeding is localized in a special organ, for instance the brain, a persisting defect may follow. These secondary defects can develop with every haemorrhage and are not necessarily caused by the therapy with anti-coagulants.

Since dicumarol, and later dicumacyl, were available in the Netherlands (1946), these medicaments came into extensive use. Some of the patients, treated by us personally, showed a serious complication which was entirely new to us. As our attention became focussed on this complication, and after presenting the clinical facts in a medical conference (1), more cases were seen by other observers and myself (2, 3). This complication, seen only in patients treated with dicumarol or dicumacyl, can be summarized as follows:

A patient, usually female, suffers from an incident bearing no special importance (delivery, operation); in the course of this a thrombosis develops, sometimes with a lung-embolism; therapy with dicumarol or dicumacyl is started; between the 4th and 8th day (a very important feature), a more or less large hemorrhage develops suddenly in the skin, extending to haemorrhagic infiltration of skin and subcutaneous tissues; this infiltration is very painful and surrounded by a hyperaemic reactive zone; a few days later the infiltrated tissues are necrotic, showing haemorrhagic blisters; in the course of the following weeks these necrotic tissues demarcate,

Table I.

Case	Age	Sex	Clinical Information	Indication for anti-coagulant therapy	Medication used
1	49	f.	thyroidectomy; dismissed from clinic; at home thrombosis right leg; lung embolism	postoperative thrombosis; lung embolism	dicumarol
2	37	f.	normal delivery; small postpartum bleeding; thrombosis left leg on 9th day	phlegmasia alba dolens left leg	dicumarol
3	20	f.	appendectomy for supposed appendicitis; dismissed from clinic; at home thrombosis left leg	postoperative thrombosis	dicumarol
4	29	f.	normal delivery; puerperal infection; thrombosis left leg	phlegmasia alba dolens left leg	dicumacyl dicumarol
5	28	f.	normal premature delivery; pulmonary infection (no certain diagnosis); thrombosis; lung embolism	thrombosis pelvic veins	dicumacyl
6	31	f.	normal delivery; on 9th day thrombosis, first of right leg, later also left leg; puerperal infection; infiltration in small pelvis	phlegmasia alba dolens right and left leg	heparin (first day) dicumarol
7	32	f.	normal delivery; thrombosis left leg; small lung embolism	thrombosis; lung embolism	dicumacyl
8	32	m.	Buerger's disease; migrating thrombophlebitis in whole left leg	thrombophlebitis migrans	dicumarol
9	67	f.	accidental fracture of left ankle and left shoulder; plaster of paris; normal consolidation; 1½ month later thrombosis right leg	thrombosis right leg	dicumarol
10	36	f.	gynaecologic operation with appendectomy; purulent wound infection; thrombosis in small pelvis; lung embolism; no thrombosis in legs	lung embolism; thrombosis small pelvis	dicumarol
11	21	f.	normal pregnancy; superficial phlebitis; r. calf; lung embolism twice with 14 days interval; thrombosis left leg. Dicumarol-therapy postponed because of expected delivery. Later instituted; normal delivery; no haemorrhage	thrombosis; lung embolism	heparin (first day) dicumarol
12	46	m.	idiopathic thrombosis right leg at home; lung embolism; admission to clinic	thrombosis; lung embolism	heparin (first day) dicumarol
13	43	f.	uterus myomatosus; metrorrhagias; thrombosis (no operation).	thrombosis	dicumacyl

leaving a more or less deep ulceration; finally this ulcer heals, leaving an extensive scar.

The primary disease, in which a thrombosis develops, seems to have no aetiological influence. As can be seen in Table I, summarizing the clinical facts, no special clinical entity was present in the majority of the cases.

I therefore have the impression that any disease, when complicated by a thrombosis and treated with dieumarol or dicumacyl, can lead to the discussed haemorrhagic complication. Age and sex can bear a relation to the disease and the thrombosis, but they seem to have no significance for the observed haemorrhage. As far as I can see a causative relationship is present only between the skin-manifestation and the therapy with the anti-coagulant. There is no relation to other factors — the day of onset of disease, the first signs of thrombosis or embolism, the day of operation, delivery, being bedridden, or admission to the clinic. There seemed to be no influence of the seriousness of the disease previous to the thrombosis, the fever, or type of infection. Because thrombosis arises more often in the female patient, a marked influence of sex is suggested. In what extent the female sex is more exposed can not be decided by my small series of cases.

Skin-Manifestations.

The complication affects almost exclusively the lower parts of the body, the buttocks and the legs; only one case (case 13; fig. 17, 18) showed a localisation in the mammary gland. More or less distinct entities are seen in that either the buttock (cases 1—5; fig. 1—6), the thigh (cases 6—9; fig. 12—15), or the lower leg (cases 10—11; fig. 7—11) is affected. In table II the localisations are summarized. — The skin-complication developed between the 4th and 8th day; it always started abruptly, between two visits to the patient, in many cases during the intervening night. Fortunately I was able to observe one case (10) from the very beginning (fig. 7—11). In the deeper tissues of the left calf a hard, very painful infiltration suddenly developed, with a patchy discoloration of the skin as in a subcutaneous and intramuscular haemorrhage. A few hours later an intra-cutaneous haemorrhage existed, almost circular in the middle part of the lower leg. I could observe how this haemorrhage in the skin developed by confluence of small patches, the central part forming one big haemorrhage (fig. 7). It was this picture we saw first in the other cases, because the initial phase lasted so briefly (fig. 3). The haemorrhages were of dimensions ranging from small (case 5; fig. 3) to extensive (case 1, 2, 3, 4, 6, 8, 13; fig. 1, 14, 15, 17). One to three days after the complication started, the haemorrhagic parts of the skin had a fully necrotic aspect as concluded from the black discoloration, the lower local temperature and the slight shrinking of the skin. As a consequence of this necrosis blisters containing haemorrhagic fluid invariably developed, one or two days after the skin-complication started (fig. 3, 9, and 12). The blisters were confined to the central, confluent haemorrhage, were solitary and of large dimensions. The tissue surrounding the haemorrhage showed vivid signs of inflammatory reaction such as warmth, swelling, hyperaemia and pain (fig. 1, 3, 8, 12 and 17).

By now the picture was complete, showing much resemblance to a haemorrhagic infarction. So far all patients showed the same picture, differing only in localisation or extent. — In the further course there were two alternatives:

a. when an extensive haemorrhage existed (cases 1, 2, 3, 4, 6, 8, 13), a great part

Table II.

Case	Localisation and extension of the haemorrhage	Days after starting therapy	Course of skin-affection
1	left buttock; ± 15 cm; perifocal reaction extends halfway thigh (fig. 1) small patch on right buttock	6 8	after 2 days one great, almost round, necrotic area with haemorrhagic blisters; after 12 days demarcation; 10 days later deep ulceration (fig. 2). After 2 months closed. — Healed with relatively small scar — The patch on the right buttock resorbed in a few days, without blisters or necrosis.
2	left buttock near trochanter major; ± 15 cm; decubitus of particular aspect	5	almost identical with case I
3	small haemorrhage on right buttock; 2 days later large haemorrhage on left buttock	5 7	almost identical with case I
4	large haemorrhage on right buttock near trochanter major; ± 20 cm	6	almost identical with case I
5	smaller haemorrhage on left buttock; ± 13 cm (fig. 3) and right buttock; ± 8 cm; near trochanter major	5	see figs. 3—6 (with description). Healed with tiny scars
6	proximal $2/3$ part of left thigh, lateral side; 20 cm long, 17 cm wide (fig. 14)	6	after one day haemorrhagic blisters and necrotic aspect; one month later deep demarcation (fig. 15); deep ulceration; healing with skin graft
7	left thigh, adjacent to left groin; 15 cm large, 4 cm long; perifocal reaction twice as great	6	after 2 days necrosis with blisters; treated with ice-bags; 8 weeks later expulsion necrotic tissue; ulceration; healed with a scar
8	almost entire left thigh	6	almost identical with case 6, only more extensive
9	distal and lateral part left thigh, ± 15 cm; smaller haemorrhage medial side left knee, ± 7 cm. Both haemorrhages surrounded by one great perifocal reaction-zone, ± 30 cm long (fig. 12)	5	much resemblance to case 10, only more extensive and different localisation; see figs. 12 and 13 with description. Died intercurrently of heart disease
10	middle $1/3$ part of left lower leg; almost circular; 10—20 cm wide; (fig. 7)	8	see figs. 7—11 with description
11	pretibial right leg ± 15 cm; next day right ankle and plantar; ± 7 cm (fig. 16); 3rd toe right foot; patellar region both sides; ± 10 cm	4 5	after 3 days haemorrhagic blisters on left knee, pretibial and plantar. After 6 days right knee, toe and plantar region normal. The other localisations developed into ulcers, and finally healed
12	entire penis	5	no clinical details available; died 9 days later.
13	right mamma; ± 15 cm haemorrhagic zone, surrounded by a red, inflammatory zone (fig. 17)	5	after some days haemorrhagic blisters; after 3 weeks demarcation; a deep ulcer existed after 7 weeks (fig. 18); a skin graft was applied a large scar resulted without a mamilla (fig. 19).

of the necrotic skin and subcutaneous tissue demarcated, leaving a large and deep ulceration (fig. 2, 15, 18). Only after many weeks did these wounds heal; the scars were exceptionally small, compared with the defect;

b. smaller haemorrhages were more patchy and irregular, with spider-like formations (cases 5, 9, 10 and 11; fig. 4, 10, 11). Some cases showed multiple localisations (5, 9, 11; fig. 5, 16). The initial phase was soon followed by disappearance of the reactive zone and complete absorption of many peripheral small haemorrhages (fig. 4, 10, 13). The much smaller central haemorrhage either was resorbed gradually without demarcation or ulceration (case 9, 10, 11; fig. 11), or showed a small demarcation and a tiny ulcer (case 5, fig. 6).

In three cases I could observe how even the central haemorrhage was partly resorbed, disintegrating into smaller patches (case 5, 9, 10; fig. 5, 11, 13).

The cases 6 and 9 can be considered as intermediate between the two groups. A rather extensive necrosis was largely resorbed. A small ulceration was present in case 6; case 9 died intercurrently. The cases 1, 3, 5 and 11 showed a bilateral localisation.

Influence of the Thrombosis.

It was tempting to regard the thrombosis as an important factor. For the cases 6, 7, 8 and 11 this seems true, because the haemorrhage developed in the same leg as where the thrombosis began. In case 9 a thrombosis was present in the other leg, whereas in case 10 no signs of thrombosis were found in the legs. For these last two cases a thrombosis without clinical symptoms could not be excluded. For the first five cases, with a localisation in the buttocks, and cases 12 and 13 localised in the penis and in the mammary gland, a thrombotic influence seems excluded. These parts showed no signs of thrombosis and are very seldom involved in this disease.

In the literature or text books no description is given of circumscribed haemorrhages with necrosis in the skin, in arterial or venous thrombosis, even in large vessels such as the aorta abdominalis or vena cava inferior. It is therefore my opinion that the thrombotic disease has no aetiological influence.

Other Influences.

None of the patients had a trauma of any severity. The localisation in the buttocks opens the possibility of decubitus. After careful consideration of all possibilities I concluded that decubitus played no rôle. None of the patients received an injection on the site of the haemorrhages. As no special type of infection predominated (except thrombosis, if this is considered as an infection) no rôle was ascribable to bacterial invasion. Venous congestion seemed to me to have a possible influence. In some cases, in association with a decrease of the temperature and increased swelling of the leg (occlusion of a large vein), the haemorrhage developed. On the contrary various other patients did not show the slightest venous congestion in the haemorrhagic area.

Table III.

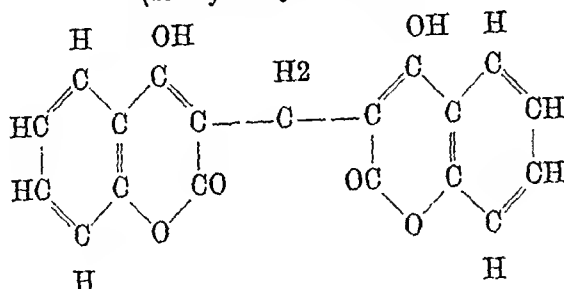
Case	Day of Therapy	1	2	3	4	5	6	7	8	9
1	Dicumarol Prothr. index Haemorrhage	300 1.2 —	100 1.8 —	100 2.2 —	100 2.5 —	— 3.7 —	50 — left side	50 4.3 —	— 4.2 —	— 4.3 —
2	Dicumarol Prothr. index Haemorrhage	300 — —	100 — —	50 2.4 —	50 2.6 —	— 3.2 left side	50 2.7 —	100 1.6 —	— 3.6 —	50 — —
3	Dicumarol Prothr. index Haemorrhage	300 — —	— 2.0 —	100 1.7 —	100 1.8 —	150 1.7 right side	100 2.0 —	100 2.4 left side	50 2.8 —	50 2.8 —
4	Dicumarol Prothr. index Haemorrhage	1000 150 —	600 150 1.3	200 100 2.0	— 150 2.1	— 100 2.1	— — 1.9 right side	— 50 2.4	— 100 1.9	— 50 2.2
5	Dicumarol Prothr. index Haemorrhage	1200 — —	1200 1.3 —	800 1.6 —	800 1.5 —	200 3.0 left and right side	— 2.7 —	800 1.2 —	600 1.6 —	100 3.0 —
6	Dicumarol Prothr. index Haemorrhage	300 — —	200 ±2.0 —	50 3.6 —	— 5.0 —	— 7.0 —	— 5.9 left side	— 4.7 —	— — —	— — —
7	Dicumarol Prothr. index Haemorrhage	200 — —	600 — —	600 1.7 —	400 2.3 —	600 2.0 —	200 1.9 left side	— 2.9 —	— 2.8 —	— 1.3 —
8	Dicumarol Prothr. index Haemorrhage	150 — —	200 — —	200 1.8 —	200 — —	200 1.5 —	— — left side	— 2.3 —	— 1.5 —	— 2.5 —
9	Dicumarol Prothr. index Haemorrhage	200 — —	300 — —	300 1.4 —	300 — —	100 2.6 left side	— — —	— 3.0 —	— — —	— — —
10	Dicumarol Prothr. index Haemorrhage	300 1.2 —	150 1.7 —	150 1.7 —	200 2.3 —	200 2.1 —	100 2.9 —	100 — —	— 4.7 left calf	— 4.5 —
11	Dicumarol Prothr. index Haemorrhage	100 — —	150 — —	200 1.1 —	— — right leg	— 1.2 right ankle, right foot	— — —	— — —	— — —	— — —
12	Dicumarol Prothr. index Haemorrhage	? — —	? — —	? — —	— 2.8 —	— — entire penis	— 2.0 —	— — —	— — —	— — —
13	Dicumarol Prothr. index Haemorrhage	1200 0.94 —	1200 — —	1200 1.4 —	1200 — —	— 1.6 right mamma	— — —	— — —	— — —	— — —

Influence of Anti-Coagulant Therapy (table III).

Up to date the complication has been seen only in patients treated with dicumarol or dicumacyl, substances with the following structural formula:

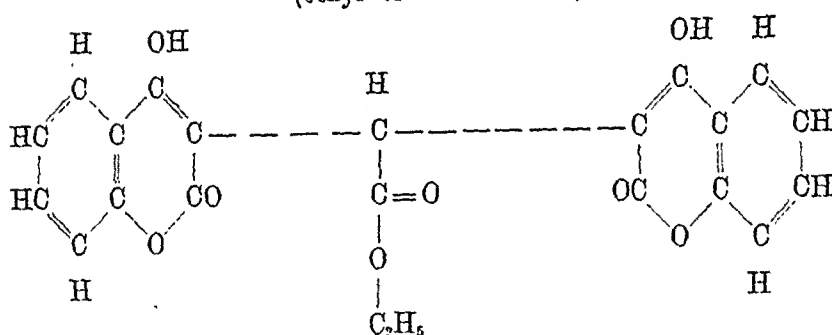
DICUMAROL

(bis-hydroxycoumarin)



DICUMACYL

(ethyl bis-coumacetate)



Possibly the other anti-coagulants have not been used in a sufficient number of cases to observe similar reactions. With the following consideration in mind it seems to me almost certain that the anti-coagulant is the causative factor. The described manifestations in the skin have hardly ever been observed under other circumstances. With a severe local trauma, or in the Arthus-experiment, haemorrhagic necrotic lesions can develop but are rarely seen. A strong positive argument is the time-relation; in eleven of the thirteen patients the first symptoms of the complication were observed between the 5th and 6th day after starting the therapy. A strong negative argument is that in patients under similar clinical conditions, but without dicumarol-therapy, the complication has never been seen. Neither haemorrhagic tendencies, including those caused by heparin or fibrinogen- and vitamin-K deficiency, nor more or less extensive thrombosis with venous congestion, ever showed complications similar to those under discussion.

By what mechanism the anti-coagulant exerts its effect is not clear. The decreased plasma-prothrombin level cannot explain why the complication is so rarely seen, nor account for the localisation, the solitary manifestation or the

necrosis. In the cases 1, 2, 6 and 10, the prothrombin level was below therapeutic limits and could provoke haemorrhages. Yet none of the patients showed haemorrhagic tendencies elsewhere in their body; (the haematuria is discussed below). A number of other patients showed only a small decrease of plasma-prothrombin at the moment the complication started. Other patients, not mentioned here, who had very low prothrombin-levels with haemorrhagic tendencies in different organs, later in the course of the dicumarol-treatment, showed no such skin-complications. For this I advance the explanation that the period during which the complication could develop (first eight days of the therapy) had passed.

The full clinical picture showed a great resemblance to a haemorrhagic infarction. There seem to be two possible explanations concerning the pathogenesis of the haemorrhage: arterial occlusion with secondary haemorrhagic infarction, or an extensive bleeding provoking tissue-necrosis with arterial compression or spasm. The last possibility seems to me to be the less probable; large intra- and subcutaneous haemorrhages (haemophilia, thrombopenia) never produce necrosis of the skin. In some cases (5, 7 and 11) the haemorrhage was too small to explain a necrosis. Therefore an arterial occlusion seems more probable, but it was impossible to correlate the arterial branches with the localisation and extension of the necrosis. The small patches of necrosis, sometimes almost surrounding an area of normal skin (fig. 9), imply localization of the arterial occlusion in very small superficial arteries. The latter feature is reminiscent of allergic phenomena.

A curious observation seemed to confirm that functional vascular factors may play a rôle. One patient, not mentioned in the tables, showed on the 4th day of dicumarol therapy a patch in the skin near the right trochanter major. The skin patch was pallid, slightly swollen and infiltrated, 7 cm in diameter, resembling a large urticarial quaddle. Some blue-yellow discoloration raised the suspicion of a small extravasation. The temperature was lower than the surrounding skin. After 4 days all symptoms disappeared. The dicumarol was administered continuously; the prothrombin-index did not exceed 2.4. The cases 1 and 3 showed a small haemorrhage on the right buttock, not necrotizing. They form intermediate cases between the one just mentioned and the full necrosis.

In six cases (1, 2, 3, 5, 7, 10) the anticoagulant therapy was continued, partly because the haemorrhage was not attributed to the medicament, partly because the danger of embolisation seemed greater than the skin-affection. In none of these patients did the skin-complication become worse or more extensive, and the course was almost the same as when the anticoagulant therapy was stopped. I had a strong impression that once the skin complication was present the anticoagulant could do no more harm.

Clinical Observations.

The course of the disease for which the patients were admitted to the clinic showed no peculiar features. The thrombosis also followed a course according to what could be expected. Routine laboratory investigations showed no deviations from expected values. The count of erythrocytes, leucocytes, platelets, the dif-

ferential count, bleeding- and coagulation-time were within limits according with the original disease or the pre-treatment values. At the time of the haemorrhage no abnormality was found in the haemostatic mechanisms except for the prothrombin time. The body-temperature at the moment of the haemorrhage and on the days before and after showed no deviations which could not be explained by the original disease. — To summarize, the patients could be regarded as routine cases, were it not that the peculiar haemorrhage with necrosis developed.

Special attention was paid in a number of the patients to haematuria. Only one (case 5), showed a macroscopic haematuria on the same day as the cutaneous haemorrhage. The prothrombin time was 3.0 times the normal. One (case 4) had a microscopic haematuria on the day of the skin-affection, and on the next two days. The prothrombin times were 1.9, 2.4 and 1.9 times the normal value. The patients 1, 2, 6 and 10 showed no marked haematuria despite high prothrombin times.

Dosage and Control of the Anticoagulant-Therapy.

In table III the medicament used and the dosage on the different days are summarized. The prothrombin times were estimated by the bedside test (1 ml venous blood + 0.1 ml thrombokinase) in the cases 1—3, 5—8 and 10—12 or by the recalcification-method (cases 4, 9, 13). The prothrombin times were calculated as values relative to normal controls; therefore only the prothrombin index is mentioned (prothrombin time of the patient divided by the normal control). All estimations were approximate, and not of scientific exactitude.

Therapy.

No particular effects were observed from different measures to diminish the skin-affection. The continuation of the dicumarol or dicumacyl-therapy had no unfavourable effect. A blood transfusion or vitamine K injections in some of the cases had no result. In one case ice-bags were used, resulting probably in a decrease of the extent of the ulceration. For the other cases a routine wound-treatment was given. A needle-aspiration was performed in case 8 on three sites in the haemorrhage. No bloody exudate could be withdrawn. Three patients received a skin graft, following a usual course.

Summary.

Thirteen patients are described with a haemorrhage and necrosis of the skin and adjacent tissues between the 4th and 8th day of therapy with dicumarol or dicumacyl. The medicament is held to be the cause of this entirely new complication.

Only one case-report was found (2). At least 6 more cases were observed in the Netherlands and personally communicated to me.

Literature.

1. H. Verhagen: Ned. Tijdschr. v. Geneeskunde 1952, page 482. — 2. W. P. Plate: Ned. Tijdschr. v. Geneeskunde 1953, page 286. — 3. H. Verhagen: Ned. Tijdschr. v. Geneeskunde 1952, page 1578. — M. U. Wiersema:

I am very much indebted to the following colleagues, who communicated their observations to me:

Dr. Duyzings, Rotterdam (case 4); Dr. Ruitinga, Hilversum (case 5); Prof. Dr. v. Bouwdyk-Bastiaanse, Amsterdam (case 6); Dr. Falger, Bussum (case 7); Dr. Melchior, Delft (case 8); Dr. Hulst, Baarn (case 9); Dr. v. d. Blink, Eindhoven (case 11); Dr. Schreuder, Sneek (case 12); Dr. Beaumont, Helmond (case 13).

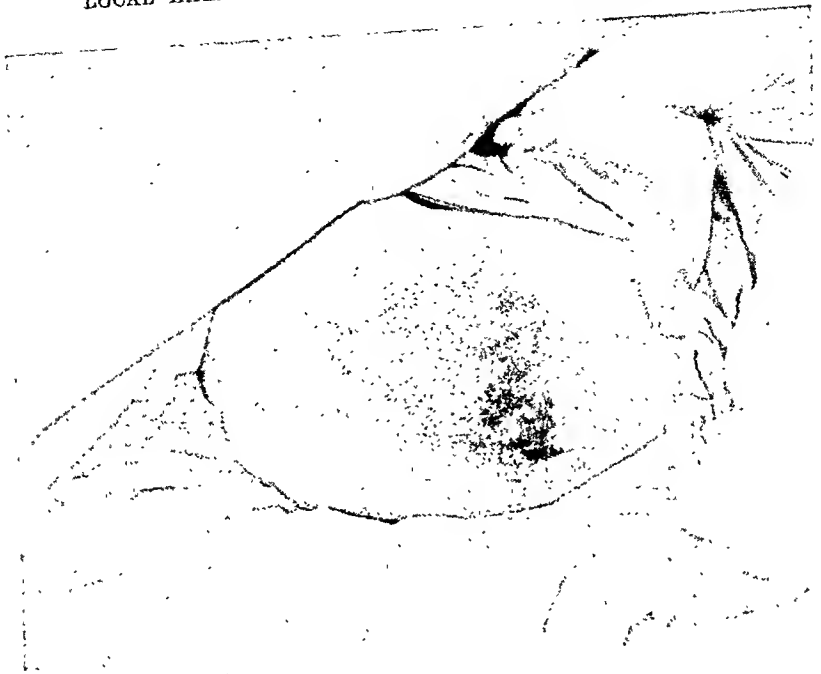


Fig. 1, 2. Case 1. Female, 49 years. Postoperative thrombosis in the right leg. On the 8th day of dicumarol-treatment a large haemorrhage developed in the left buttock, near the trochanter major. — Fig. 1: 10th day of treatment; large haemorrhage with a reactive zone. A large blister was previously drained; it lay flat on the haemorrhage. — Fig. 2: after demarcation and expulsion of the necrotic tissue on the 25th day of treatment; large and deep ulceration. The reactive zone almost disappeared. — The photographs of case 4 are exactly the same.

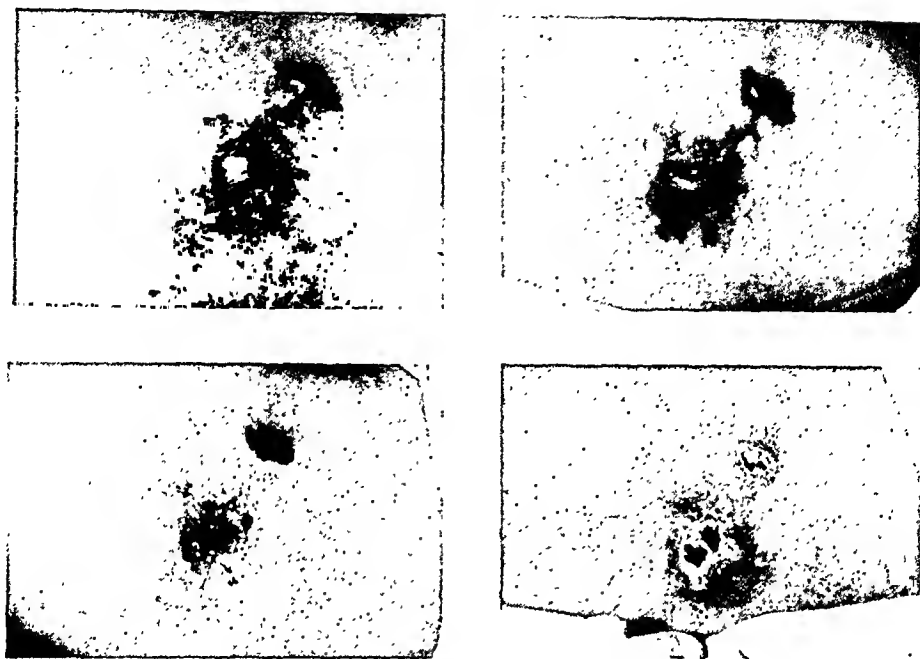


Fig. 3, 4, 5, 6. Case 5. Female, 28 years; thrombosis post-partum and lung embolism. The localisation of the thrombosis was first not clear. Both legs were free from thrombotic symptoms. On the fifth day of dicumacyl-therapy a small haemorrhage developed on both buttocks, near the trochanter major. The left leg showed by now signs of thrombosis. The dicumacyl-treatment was continued throughout the disease. — Fig. 3: left buttock on the seventh day of treatment; small haemorrhage, in two areas, each with a blister; many tiny haemorrhages showing how the large haemorrhage developed by confluence. — Fig. 4: three days later; tiny haemorrhages almost disappeared; spider-like large haemorrhage; reactive zone much smaller. — Fig. 5: four days later; blisters empty; haemorrhage much smaller with some necrosis and healing of the skin; still some subcutaneous infiltration. — Fig. 6: four days later, 18th day of therapy; two small ulcers with remnants of necrotic skin. — The affection on the right buttock followed exactly the same course.

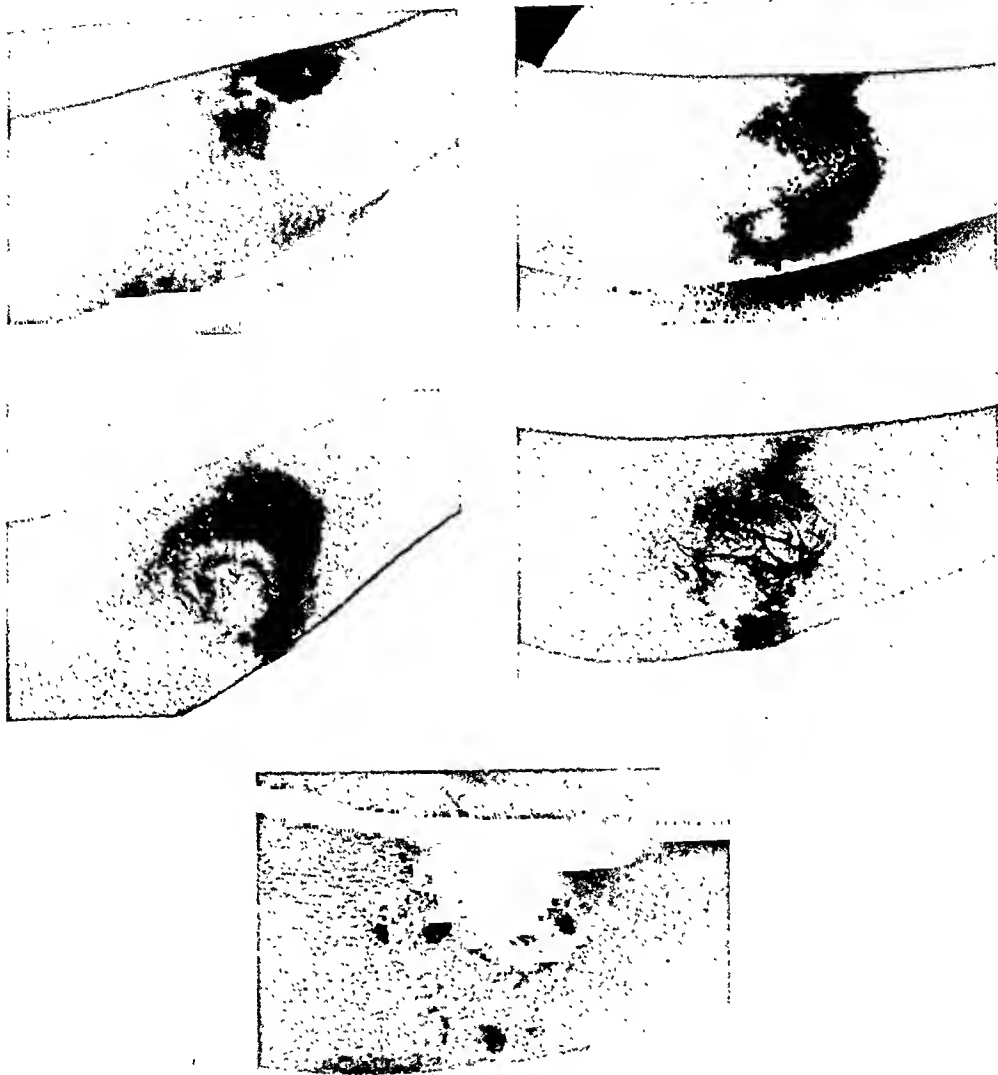


Fig. 7, 8, 9, 10, 11. Case 10. Female 36 years. Appendectomy and ablation of adhesions. Post-operative high fever; twice lung embolism without signs of thrombosis in the legs. On the eighth day of dicumarol-therapy a haemorrhage developed in the left calf. — Fig. 7: 8th day of therapy; large haemorrhage, patchy on the ventral side, confluence on the dorsal side of numerous small haemorrhages; extensive infiltration of the surrounding tissue. — Fig. 8: next day; partial resorption of the haemorrhage in the periphery; start of blister formation; large reactive zone. — Fig. 9: next day; blisters with haemorrhagic content; irregularly shaped necrosis surrounding an area of normal skin; infiltration and reactive zone partly resorbed. — Fig. 10: 20th day of dicumarol-therapy; the blister is removed; in large part the necrotic areas have been replaced by young skin, leaving a number of small, irregular, necrotic patches. — The skin affection healed completely without ulceration. — Throughout the disease no signs of venous obstruction in the legs were seen.

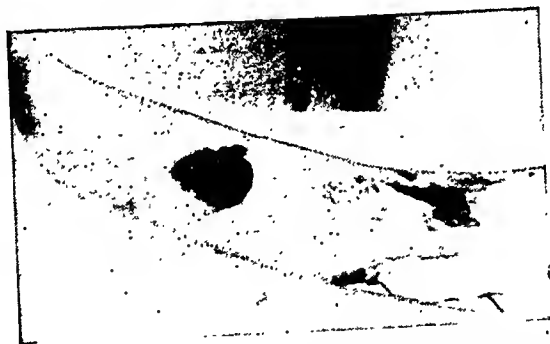


Fig. 12, 13. Case 9. Female, 67 years. Accident with a fracture of the left shoulder and ankle; 45 days later thrombosis of the right leg; also a myo-degeneration existed. On the 5th day of dicumarol-treatment a large haemorrhage developed on the left thigh, the lateral and distal part, and a smaller one on the medial side of the left knee. Dicumarol stopped. Fig. 12: 8th day from the beginning of dicumarol-treatment; large haemorrhage with one great blister; by now signs of thrombosis of the left leg. — Fig. 13: 22nd day; blisters empty; rather extensive, irregularly shaped necrosis; no perifocal reaction left. The patient died five days later of her heart-disease. No autopsy.

Fig. 14, 15. Case 6. Female 31 years. Parametritis and phlegmasia dolens post-partum. The dicumarol-treatment was stopped after 3 days because of overdosage. 3 days later a large haemorrhage developed in the left thigh. — Fig. 14: extensive haemorrhage on proximal, lateral part of the left thigh; the large blister is already empty. — Fig. 15: extensive necrosis with demarcation and ulceration (exact dates not mentioned).

Fig. 16. Case 11. Female 21 years; superficial phlebitis in the 7th month of pregnancy; later thrombosis of the left leg with lung embolism. On the 4th day of dicumarol-treatment, and on the following days, multiple haemorrhages developed. The treatment was stopped. The fig. shows the haemorrhages near the right ankle and on the plantar side of the foot.

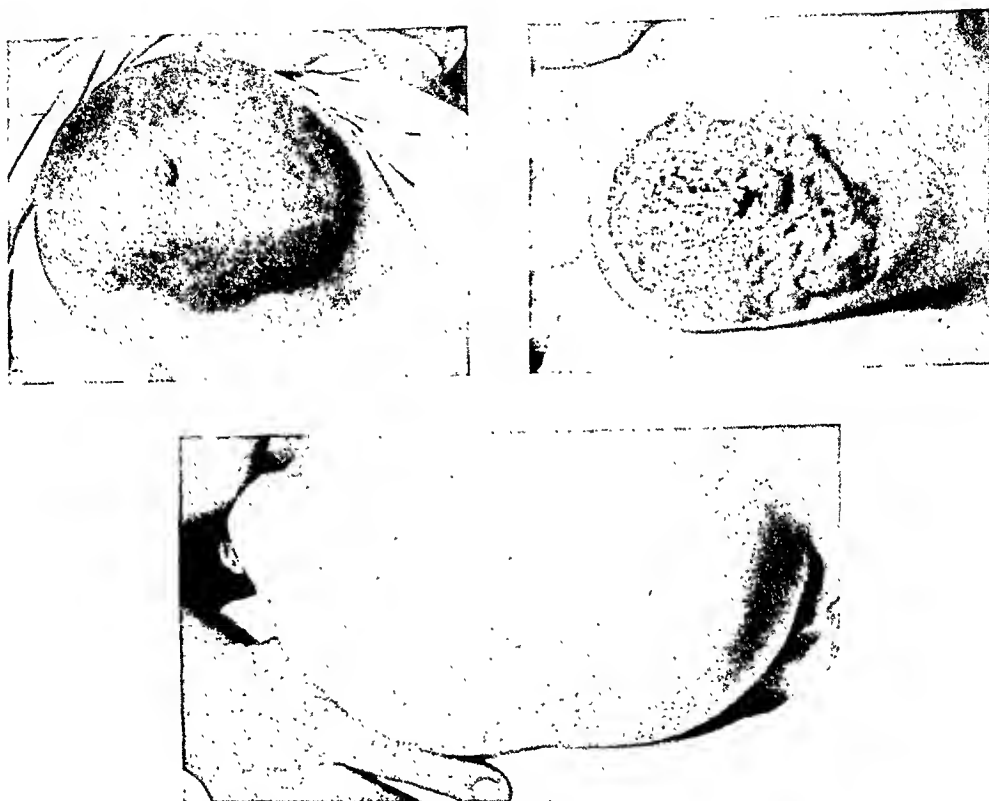


Fig. 17, 18, 19. Case 13. Female, 43 years. Uterus myomatosus with metrorrhagias and necrotic myoma. A spontaneous thrombosis developed. On the 5th day of treatment with dicumacyl a large haemorrhage developed in the right mamma (fig. 17). A hyperemic, painful zone surrounded the haemorrhage, and is just visible on the picture. After a few days haemorrhagic blisters developed. Three weeks later demarcation started, leaving a large ulcer after three more weeks (fig. 18). A skin graft was necessary to heal the large defect (fig. 19).

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The Functional Control of the RES in Patients with Undernutrition.

By

S. LIVIERATOS, E. DANOPOULOS and K. MARATOS.

(Submitted for publication October 5, 1953.)

Starting from Troschke's (1) experiments, from which it is supposed that the alcohol's metabolism should take place in the organs that control the metabolism, as well as from Fiessinger (2) and co-workers' experiments, from which it comes out that liver participates to the metabolism of this substance, the second of us (Danopoulos (3)) carried out a series of experimental studies, by which it was undoubtedly shown, that the main tissue burning the alcohol is the reticulo-endothelial one (R. E. S.). He studied the alcohols metabolism in rabbits by following its amount in the blood. This was achieved by determining the alcoholemic curve. Blocking partially the RES function with repeated injections of red ink or colloidal gold or a combination of both, he obtained higher and sometimes longer curves, which meant an incomplete combustion of the alcohol, being given that the normal alcoholemic curve is low and short. Then, having showed that the RES is the main tissue burning the alcohol, he advanced furthermore trying to realize whether the liver, which contains a considerable part of the RES, is the main organ burning the alcohol.

For this purpose, Danopoulos (4) has made comparative studies in dogs, where he determined the alcoholemic curve after oral or intravenous adminisitation of the same quantity of alcohol. In this way, the alcohol administered orally was passing through the liver before entering the general circulation, while after the intravenous injection it entered the general circulation without passing through the portal vein and the liver. The diversion from the liver in the above way gave a normal or a little higher alcoholemic curve, in comparison to the one obtained after oral administration, which means that the liver's participation to the alcohol's metabolism is not very considerable. It is clear, however, that although the liver is left beside by the intravenous injection, we cannot exclude its participation to the alcohol's metabolism, a considerable quantity of which will finally pass through the liver either through the gastric or through the intestine's blood vessels — and therefore through the portal vein or through the hepatic artery.

For this reason, Danopoulos (5) undertook another series of experiments in dogs. He excluded the liver from the circulation by means of an Eck fistula, determining the alcoholemic curve before and after establishing the fistula. He found thus that the curve was slightly or not at all impaired. It was proved therefore that the liver is not the main organ burning the alcohol but it simply participates to the alcohol's metabolism by the part of the RES that it contains.

Then, he determined the alcoholemic curve in dogs, before and after splenectomy (6). He found a much higher alcoholemic curve after splenectomy in these dogs that burned normally the alcohol before the operation. In other dogs, that did not burn properly the alcohol before splenectomy, he could not find but an insignificant alteration of the curve after this operation. This last observation leads this investigator to the thought, that the incomplete metabolism of the alcohol found before splenectomy in these animals was due to a functional insufficiency of the spleen.

According to these findings, if the RES is underfunctioning, the organism's ability to burn the alcohol should also be impaired. On the opposite, if the RES is overfunctioning, the alcohol should be burned more rapidly than usually. This was confirmed with Danopoulos (7) experiments in feverish patients, where it was found that alcohol is burned in these cases with a double speed than usually; the thought, that the RES is overfunctioning during the fever, was thus proved to be correct.

After this brief review of the work dealing with the alcohol's metabolism, we should point out the significance of the fact that *the RES is the main tissue burning the alcohol. Determining the alcoholemic curve, we can now say, whether the cells of the RES, dispersed all over the body, are functioning well or not.*

In this way, a new method for a *functional control of the RES is provided.* An alcoholemic curve higher than the normal means an impaired function of the RES. A low curve means overfunctioning of the RES.

This method was first used to investigate the functional condition of the RES in patients with undernutrition, treated in our Clinic during the undernutrition period 1941-42.

This study was done by determining the alcoholemic curve in such patients, before and after their treatment, when this latter was successful. We always preferred the patients that did not present any evidence of coexisting cardiac or renal disease which was usually the case. No special treatment or diet was administered to these patients before the alcoholemic curve was obtained. 0.6 cc of alcohol per kg of body weight was given by mouth as a 10 % solution in water. This quantity is adequate for proper study of the alcohol's metabolism in men, for it is easily burned by the organism and has no toxic effects, causing a very mild intoxication only. For body weight we usually took the ideal weight, although in some instances the real weight was considered; no essential difference was noticed in the curves obtained.

The patients were fasting twelve hours before the administration of the alcohol. A number of patients had marked oedema (anasarka), so that we had been able to measure the quantity of alcohol not only in the blood but in the oedematic fluid

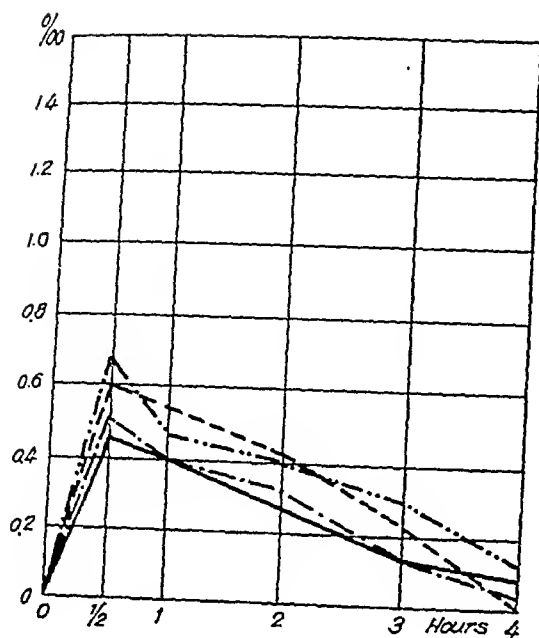


Fig. 1

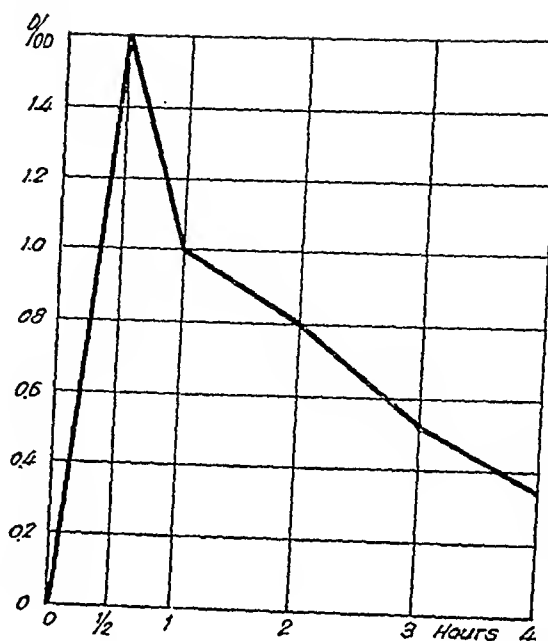


Fig. 2

too, after puncturing the swollen foot or leg, or even the peritoneal cavity, in case an ascites was present. Blood or transudate was obtained twice every half hour and then 2, 3 and 4 hours after the administration of the alcoholic solution. The volume of blood or transudate was measured with an accurate pipet (0.10 mm each time) according to the Widmark (8) method, modified by Kanitz (9).

Experimental studies. Forty patients with undernutrition were tested. The first group of 23 had slight or no oedema at all; therefore we determined the alcoholemic curve only. The second group consisted of 17 patients with marked oedema.¹ In this latter we followed not only the alcoholemic curve, but the quantity of alcohol in the oedematic fluid as well; otherwise the study of the metabolism would be incomplete.

Before starting with the description of some of our experiments, we give in fig. 1 the alcoholemic curves of four normal individuals. It clearly appears there, that the normal organism burns almost the total of the quantity administered in 4 hours; the highest point of the curve does not exceed 0.65 ‰. The differences between individuals are insignificant.

First group: Patients with minor — or without any oedema. We present here three characteristic alcoholemic curves, out of the 23 tested cases.

In case 1, a male patient aged 52 had been receiving inadequate food for 6 months. Body weight: 40 kg; ideal weight: 51.6 kg. The alcoholemic curve was found extremely

¹ It is well known that in patients with undernutrition, marked oedema is sometimes present. Nevertheless, there is also a so-called dry form of the disease with slight or even without any oedema.

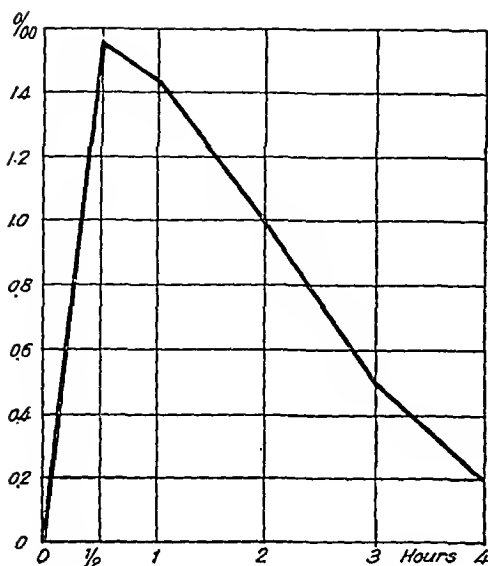


Fig. 3

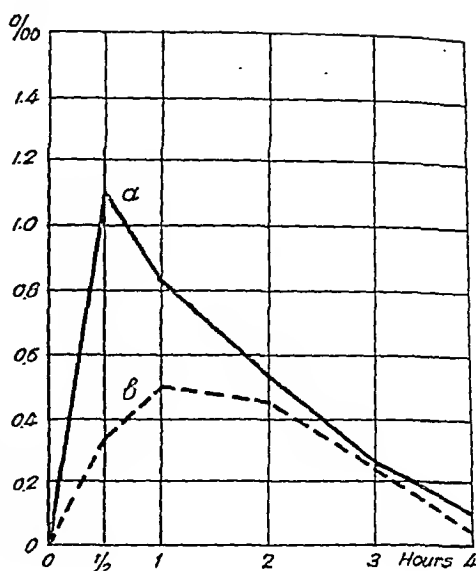


Fig. 4

high and prolonged as well (compare fig. 2 to the normal curves of fig. 1). A considerable quantity of alcohol was found in the blood, even during the fourth hour.

In the second case, a male patient 35 years old, without any past history, had been suffering from undernutrition for 6 months. Body weight: 40 kg; ideal weight: 52.7 kg. The quantity of alcohol given, was proportional to his ideal weight. The curve shown in fig. 3 demonstrates here also, how impaired was, the organism's ability to burn the alcohol.

In the third case, a man aged 62, had been feeded quite inadequately for the last 6 months. One and a half month ago, he manifested clinical signs of undernutrition. His body weight was 42 kg, while his ideal weight was 55.5 kg. The quantity of alcohol administered, was proportional to the real body weight. The alcoholemic curve *a* (fig. 4) shows the impairment of the organism's ability to burn the alcohol. Curve *b* of the same figure was taken 50 days after the first, while the patient's condition had obviously improved. Therefore, the improvement of the general condition results in the restoration of the alcohol's metabolism to the normal.

Discussion.

We can now come to the conclusion, that the alcohol's metabolism in patients with undernutrition and minor or no oedema, is found impaired, the impairment being proportional to the severity of the undernutrition and its effect on the economy of the organism in general. The greater the effect of undernutrition, the higher the alcoholemic curve was. On the opposite, the lesser the organism was affected by undernutrition, the lower the curve was, approaching thus the normal height; in other words, the alcohol's metabolism was easier in this organism. These alcoholemic curves remind us of those obtained after blocking the RES in rabbits, as it had been experimentally done by the second of us. The simi-

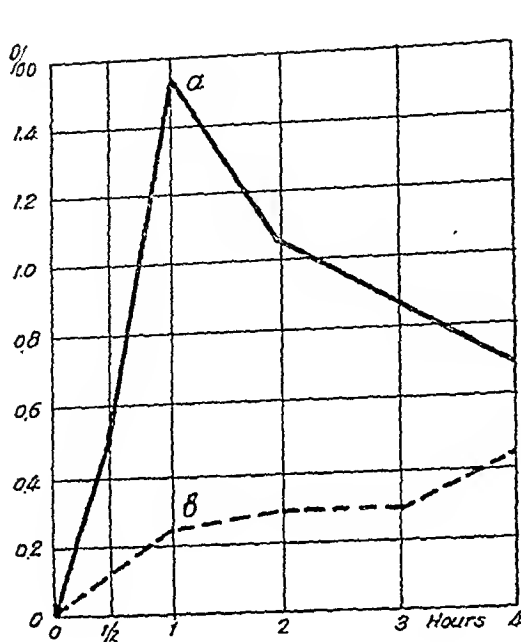


Fig. 5

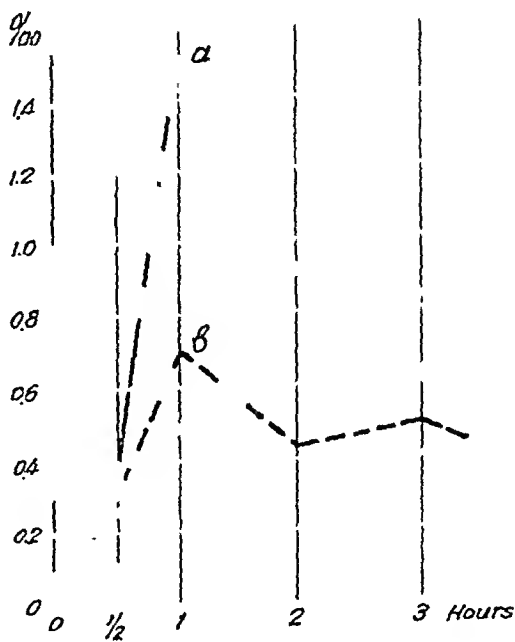


Fig. 6

larity of the curves in both cases is really amazing. In these lastly mentioned experiments the alcoholemic curve was found higher when the RES was blocked completely after repeated injections of drawing ink or colloidal copper. So we can undoubtedly speak of an impairment of the RES-function in our patients with undernutrition. We could also use the alcoholemic curve for prognostic purpose, since the impairment was parallel to the severity of the patient's condition. It should also be noticed that when the patient's condition was severe and the curve high, the alcohol intoxication was marked and of long duration, while in normal individuals this small quantity of alcohol causes only a slight dizziness starting 5'—15' after the administration and disappearing completely one to one and a half hour later.

Second group: Patients with marked oedema. Four curves are presented out of 17 similar cases.

Case I. A male patient, aged 56, without any past history, had been receiving inadequate amount of food for the last 5 months. Three months ago he started having oedema, which gradually increased and became recently very marked. Body weight: 60 kg. Ideal body weight: 62 kg. The small difference between the real and ideal body weight is certainly due to the oedema. The quantity of alcohol given, was proportional to his real weight (60 kg). Curve *a* (fig. 5) shows the quantity of alcohol in the blood; curve *b*, the amount contained in the oedematic fluid. It is clearly shown with these curves, that the impairment of the alcohol's metabolism in this patient is greater than in the 1st group patients (undernutrition without oedema). The patient of this case died a few days later.

Case II. Male, 66 years old, receiving inadequate food for 8 months. Five months ago, loss of strength, minor oedema. Fifteen days ago, the oedema became very marked.

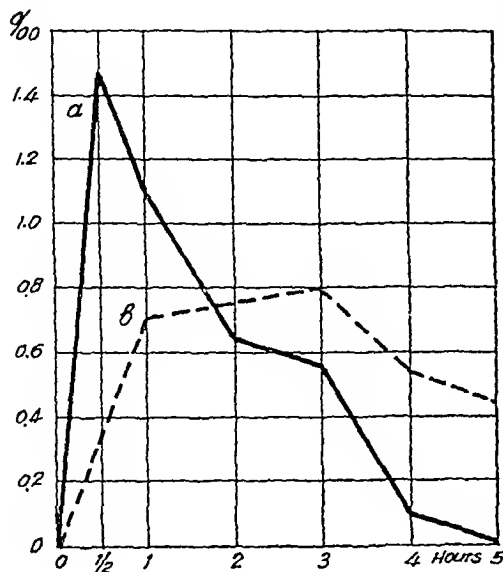


Fig. 7

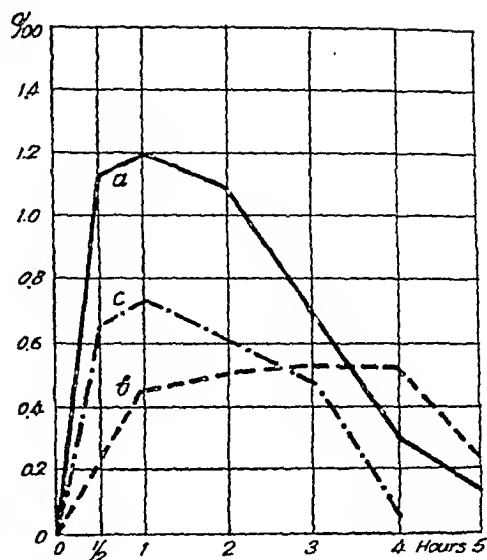


Fig. 8

Body weight 44 kg. Ideal weight 57.1 kg. The quantity of alcohol given was proportional to the ideal weight. The alcoholemic curve *a* and the curve of the alcohol in the oedematic fluid (*b* — fig. 6) present evidence of the enormous impairment of the organism's ability to burn the alcohol. This patient died also, although his food in the clinic was relatively good.

Case III. A male patient, 66 years old, without any past history, had been receiving inadequate food for 6 months. Two months ago he started having oedema that became marked 15 days ago. Nevertheless, he did not have a marked loss of strength. Body weight: 48 kg. Ideal weight 58 kg. The alcohol was given in a quantity proportional to his ideal weight. The alcoholemic curve *a* of fig. 7 is extremely high; however, it goes down rather quickly, so that in the fourth hour, only a small quantity of alcohol was found in the blood. Curve *b* of the same figure is high and goes down slowly, so that it crosses curve *a*. This means, that the rapid descent of the alcoholemic curve is due to some extent to the fact that the alcohol was burned by the organism; but an important part of it is coming out of the blood to the oedematic fluid, from which it is given back to the tissues, to be gradually burned. This patient survived and was discharged with minor oedema, after long treatment. This crossing of the curves is observed in 15 out of the 17 cases. In 2 cases, where the curves did not cross each other and remained parallel, the patients died.

Case IV. A male patient aged 18, had been receiving inadequate food for 5 months. One month ago, oedema appeared and became very marked 10 days ago. Body weight: 45 kg. Ideal weight: 50 kg. The quantity of alcohol was proportional to his ideal weight. Curves *a* and *b* of fig. 8 show clearly the impairment of the alcohol metabolism in this patient. Curve *c* of the same fig. was taken 21 days after the first experiment, after the patient had been cured. This curve shows the alcohol metabolism restored almost to the normal.

Discussion.

From the study of this group we come to conclusions similar to those of the previous one. The only difference is that the alcohol metabolism in this last series was more difficult, for a part of the alcohol diffused from the blood into the oedematic fluid, and then was given again to the tissues to be burned.

In the first two cases, where curves *a* and *b* were parallel without crossing each other, we cannot talk about any significant ability of the organism to metabolize the alcohol. Four hours after the administration, the alcohol was still found in the blood and the oedematic fluid as well, in considerable quantities. Therefore, the severity of the condition is easily estimated, with a simple glance on these curves. This was true from the clinical view point too, since both patients died, a short time later. In other cases — not presented here — the alcoholemic curve was high and descended to the zero-line, 5 hours after the administration of the alcohol; this does not mean that the alcohol was burned. It was simply concentrated into the oedematic fluid and this is why curves *a* and *b* cross each other. Quite a big amount of alcohol is still found in the oedematic fluid of these patients, 5 hours after its oral administration. Consequently, the disturbance of the metabolism was considerable in these patients, because undernutrition had considerably affected the general economy of the organism. How does it happen now, to find no alcohol in the blood, although a big quantity of it was found in the oedematic fluid where it persisted even during the 4th or 5th hour after the administration? We think that this fact can be explained as follows: The alcohol enters the circulation after its quick absorption; a part of it starts getting burned by the RES of the central organs (liver, spleen, lymph nodes, bone-marrow). Another part diffuses into the oedematic fluid, wherefrom it is taken by the peripheral RES and is burned slowly, because due to the oedema this particular part of the RES is more insufficient than that of the central organs. Thus, it disappears quicker from the blood than from the oedematic fluid. This is also why the disturbance of the alcohol metabolism is much greater in the patients of the second group than in those of the first one (without or with slight oedema). The alcohol intoxication signs manifested by the patients of the second group were more intense and of longer duration, depending on the difficulty to metabolize the alcohol.

Summary and Conclusions.

The following conclusions can be drawn from the whole study.

1. The organism's ability to burn the alcohol is considerably impaired in patients with undernutrition. The degree of impairment depends on the severity of the patients' condition.
2. The disturbance of the alcohol metabolism is greater in patients with undernutrition presenting marked oedema.
3. The quantitative determination of alcohol in blood or in the oedematic fluid, if there is any, can be used as a prognostic sign for the severity of the condition and its possible development.

4. The function of the RES is more or less considerably impaired in patients with undernutrition, depending on the severity and the duration of the disease.

5. Finally, the use of alcohol as a calory-producing substance should be avoided, especially in this type of patients.

Literature.

1. Troschke, G.: Pflügers Arch. 235, 785 (1935). — 2. Fiessinger, N., Benard, H., Courtial, J., Dermer, L.: C. r. Soc. Biol. Paris 122, 1255—1258 (1936). — 3. Danopoulos, E.: Z. f. d. ges. exp. Med. 103, 212—221 (1938). — 4. Danopoulos, E.: Z. f. d. ges. exp. Med. 106, 374—376 (1939). — 5. Danopoulos, E.: Z. f. d. ges. exp. Med. 106, 396—400 (1939). — 6. Danopoulos, E.: Z. f. d. ges. exp. Med. 106, 401—405 (1939). — 7. Danopoulos, E.: Z. f. d. ges. exp. Med. 106, 406—408 (1939). — 8. Widmark, E.: Biochem. Z. 131, 473 (1922). — 9. Kanitz, H.: Z. f. d. ges. Ger. Med. 24, 273—274.
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From the 1st Med. Clinic of the Athens University. Director: Assoc.
Professor E. Danopoulos.

The Functional Impairment of the Reticulo-endothelial System in Patients with Bronchial Asthma.

(An experimental study)

By

S. LIVIERATOS, E. DANOPOULOS and K. MARATOS.

(Submitted for publication October 5, 1953.)

Continuing our efforts to determine the functional control of the reticulo-endothelial system (RES) in several diseases, we studied this time the alcoholemic curves in patients with bronchial asthma. The technique used was the one described in previous reports.

Our experiments were performed on ten patients. These cases were carefully selected, so that they would be free of any evident disturbance that could possibly affect the alcohol's metabolism. Eight of them were suffering from typical bronchial asthma (one was a light case). One of the remaining two patients was suffering from chronic bronchitis with marked emphysema, causing paroxysms of dyspnoea, of moderate intensity. The other one was suffering from marked emphysema and had for long time symptoms of right heart failure. Dyspnoea in this patient was primarily due to emphysema. The experiment was performed on these last two patients with the intention to compare their curves with those of the other patients, four of which showed rather marked eosinophilia. The description of the cases and the results of this research will account for this comparison.

We are here presenting three of our cases. The description of the remaining is omitted because the results were similar. For the same reason we are only presenting one of our two cases with emphysema.

Case 1. A patient, 52 years old, was suffering from repeated attacks of bronchitis, occurring more frequently during the winter months. In the last five months before his present disease started, he had three such attacks. One and a half month ago, he had the first typical paroxysm of bronchial asthma, that lasted a few hours. Since then, he had daily paroxysms of dyspnoea. The last paroxysms were related by the patient to the smelling of flowers or the ingestion of certain food.

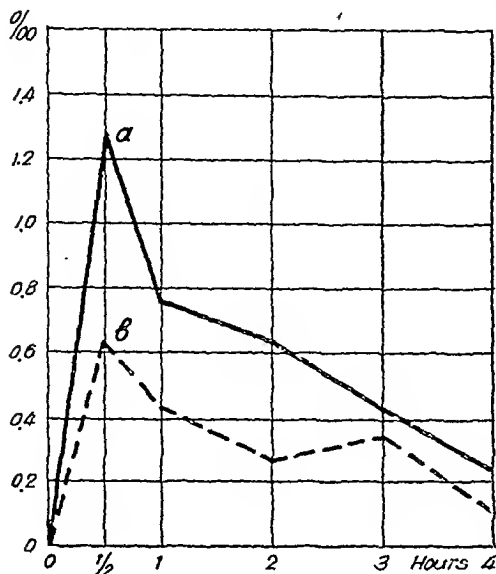


Fig. 1.

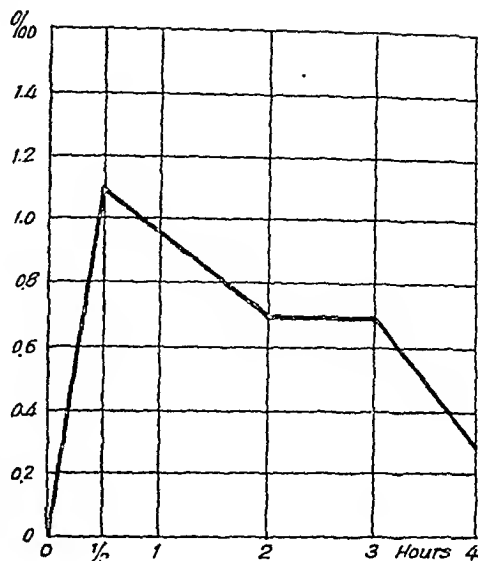


Fig. 2.

The physical examination revealed signs of moderate pulmonary emphysema, abundant dry râles and marked prolongation of the expiration. Laboratory examinations: White blood cells: 9,200 per cmm. Blood eosinophils: 11 %. Eosinophils and Curshmann's spirals were not found in the sputum.

The first alcoholemic curve was obtained six days after the admission. The curve appears high; four hours after the alcohol's administration, it was still found in the blood, in considerable quantities. It should be noticed that the experiment was carried out while the patient was suffering from intense dyspnoea. Fifteen minutes after the administration of the alcohol, the dyspnoea had stopped and reappeared with a smaller intensity three hours later. The patient manifested signs of alcohol intoxication. 57 days later, another curve was obtained. In the meantime, the patient was in excellent condition for almost one month. Curve *b* of fig. 1 is normal and demonstrates that the alcohol metabolism was completely restored.

Case 2. This was a patient, 65 years old. From his past history we retain that for 20 years he had symptoms of adenoids and also the fact that he is a heavy smoker. The present illness started 25 years ago with frequent bronchitis attacks; an expiratory type dyspnoea appeared approximately at the same time. The first paroxysm of bronchial asthma occurred in 1941. Since 1941, paroxysms of different intensity occurred at irregular time intervals. During the last five months, the patient was suffering from a continuous dyspnoea of the expiratory type. The physical examination revealed a moderate emphysema and abundant dry râles. Blood eosinophils: 1 %.

Fifteen days after the admission, while the patient was continuously dyspnoic, an alcoholemic curve was obtained, which is shown in fig. 2. This curve is considerably high and goes down slowly, so that three hours after the ingestion of alcohol the blood still contains 0.68 %/100. This last fact proves the considerable impairment of the patient's capability to burn the ethylic alcohol. On this patient, dyspnoea had also stopped twenty minutes after the ingestion of the alcohol and reappeared three hours after the beginning of the experiment. During these three hours, the patient manifested signs of alcohol intoxication. The experiment was not repeated in this patient, for he did not show any noteworthy improvement of his condition.

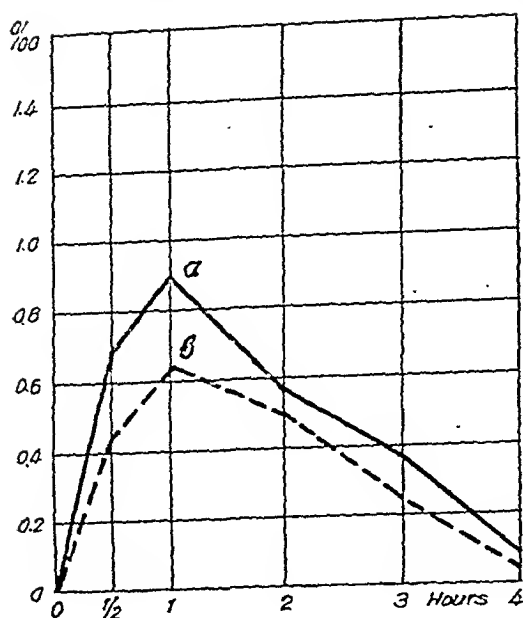


Fig. 3.

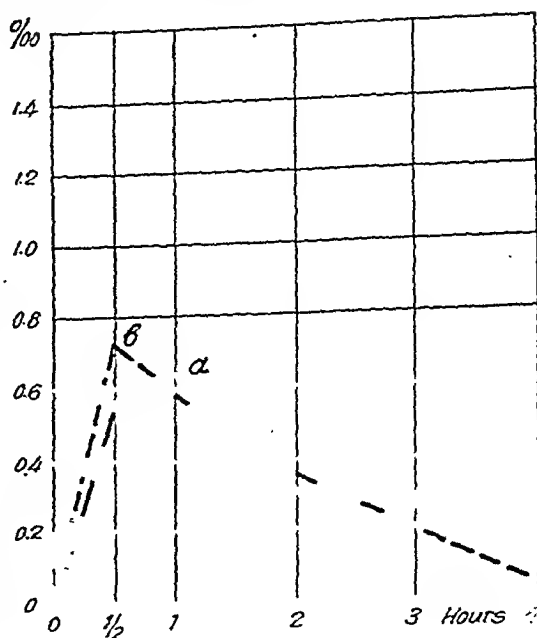


Fig. 4.

Case 3. A patient, aged 45, started three years ago with a typical paroxysm of bronchial asthma lasting two hours. The attacks were repeated in several time intervals. Two months before admission, her condition deteriorated. Physical examination: Moderate emphysema and abundant dry râles. Blood eosinophils: 8 %. White cells: 9,800 per cmm.

The curve *a* of fig. 3 was obtained 25 days after the admission, while she was still suffering from paroxysms of minor intensity. The curve is higher than the normal and progresses slowly; it shows thus the incomplete metabolism of the alcohol. Signs of moderate intoxication appeared during the first three hours.

Curve *b* of fig. 3 was taken 40 days after the first, while the patient was not having any dyspnoea for 15 days. This curve is normal, so that we can conclude that the patient was restored to the normal, independently of the clinical cure.

Case 4. A 68 years old patient had repeated attacks of bronchitis for many years and particularly during the winter months. His present illness started 12 years ago with a paroxysm of expiratory dyspnoea that lasted one hour and was accompanied by cough and mucopurulent sputum. Similar paroxysms occurred from time to time and became recently more frequent; they were characterised by abundant expectoration and low fever (up to 38° C). Dyspnoea was always of moderate intensity.

Physical examination shows highly marked pulmonary emphysema and moist râles. White blood cells: 8,000 per cmm. Blood eosinophils: 1 %.

Five days after the admission, the patient was given the alcohol and the curve *a* of fig. 4 was drawn. This curve differs slightly from the normal, demonstrating a slight impairment of the organism's ability to burn the alcohol. The moderate dyspnoea disappeared completely half an hour after he ingested the alcoholic solution and reappeared 24 hours after the experiment.

After 26 days of bedrest and treatment of the bronchitis, curve *b* was obtained, which is quite normal. It must be noticed that even 15 days before curve *b* was taken, the patient did not have any dyspnoea and was in good general condition. The signs of intoxication in both experiments were insignificant.

Summary and Conclusions.

As it became evident of the above description of our cases, the alcoholicmic curve of patients with bronchial asthma after alcohol ingestion, is higher than the normal. There is no relation between its height and the intensity of dyspnoea. In other words, there is a functional impairment of the RES in bronchial asthma, which is not parallel to the intensity of the dyspnoea.

After the ingestion of alcohol, dyspnoea is stopped and reappears some time after the action of alcohol is over.

In patients with dyspnoea due to marked emphysema (case 4), the alcoholicmic curve is normal.

The intensity of the intoxication signs was parallel to the disturbance of the alcohol metabolism.

From the 1st Med. Clinic of the Athens University. Director: Assoc.
Prof. E. Danopoulos.

Experimental Studies of the Functional Activity of the Reticulo-Endothelial System in Patients with Allergic or Aphyllactic Urticaria.

By

E. DANOPOULOS AND B. ANGELOPOULOS.

(Submitted for publication October 5, 1953.)

Trying out the test of the functional activity of the RES in other diseases too, we studied the configuration of the alcoholemic curve (same method as in previous reports) in patients with allergic and aphyllactic urticaria, starting from the finding, that the function of the RES is impaired in patients with bronchial asthma.

We tested 14 patients, 5 of whom were suffering from acute urticaria after food poisoning, 4 had acute aphyllactic urticaria after antitoxic serum injection and 5 had a chronic urticaria of unknown etiology. In the first 8 cases, the first curve (a) was obtained during the acute stage of the disease and the second one (b) 3 to 5 days after the eruption and the other signs of the disease had completely subsided, after the proper antihistaminic and dietetic treatment. In two cases, 2 cc of Neo-antergan (N-dimethyl-aminaethyl-N-paramethoxybenzyl-X-amino-pyridin) were injected intramuscularly during the acute stage, after having taken the second blood sample, *i. e.* one hour after the ingestion of the alcoholic solution. In 3 cases, an intramuscular injection of Neo-antergan was given 1/2 hour before and 1 hour after the administration of the solution. Finally, in one case the alcoholemic curve was determined several times during the disease.

Every patient had his blood pressure taken, he had a complete examination of the urine, blood counts, blood proteins and protein quotient, Wassermann and Kahn tests; patients with chronic urticaria had a Casoni skin test, a Weinberg and other laboratory tests necessary for a complete study. In the following description of the cases, only abnormal findings will be mentioned.

From the 14 tested cases only 4 are reported here.

Case I. A male patient, 29 years old, gave us a history of typhoid fever at the age of 15. Five days after an injection of antitetanic serum, oedema appeared at the site

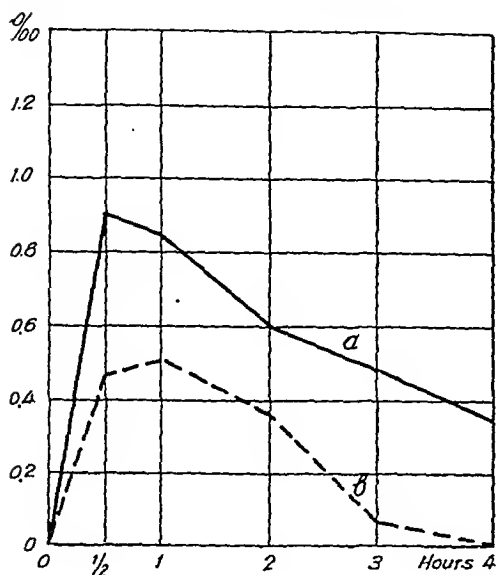


Fig. 1.

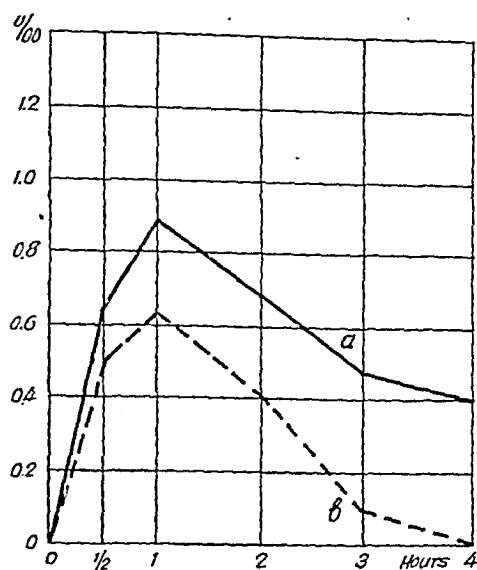


Fig. 2.

of the injection, together with erythema and a few elements of papular exanthema. Two days later the eruption was generalized; oedema of the lips and fever appeared. From the clinical examination urticaria only was confirmed. From the laboratory examinations nothing important. Eosinophils 2 %. Curve «a» (fig. 1) was obtained of the day of the admission, when the eruption was limited to the left lower limb and the temperature was 38° C. It appears moderately elevated at the beginning and the end of it, in spite of the fever. Curve «b» was taken after the complete disappearance of all symptoms; its configuration is normal.

Case II. A female patient, aged 38. The day before the admission, 3 hours after a meal of meat, a papular eruption appeared at several parts of the body, accompanied by intense pruritus. Twelve hours later the patient had an oedema of the eyelids, lips and hands, she had a feeling of malaise and a tendency to faint. From the clinical examination: papular eruption spread all over the body surface. The liver was palpable two fingers below the right costal margin. Laboratory examinations gave nothing important. Curve «a» (fig. 2) was obtained during the acute stage; curve «b», three days later, when the disease had completely subsided. Curve «a» is high from the beginning to the end, curve «b» is normal.

Case III. Male patient, 39 years old. He gave a history of syphilis and malaria at the age of 24. Five days after an injection of antitetanic serum, he felt pruritus at the site of the injection, which was spread all over his body, in a short time. Twelve hours later a papular eruption appeared at several parts of the body, accompanied by loss of strength and a tendency to fainting. Blood pressure 9/7 emHg. From the blood counts: moderate eosinophilia (7 %), without any other abnormal finding. Serum bilirubin: direct reaction (+), indirect: 0.64 mg%. Urobilinogen in the urine (++++). Few hours after the admission, at the height of the eruption, the first alcohemie curve was obtained (curve «a» of fig. 3), which was only a little higher than the normal, at the first and second half-hour. Nevertheless four hours after the administration, considerable quantities were still found in the blood. Curve «b» was taken 4 days later, when only few urticarial elements remained.

Case IV. Female patient, aged 57. She had repeated attacks of tonsillitis for many years. Every now and then, she was feeling pain at the joints with slight oedema. Eight

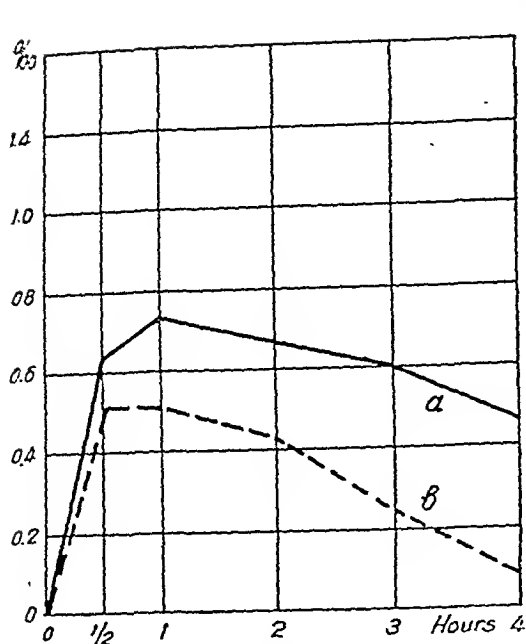


Fig. 3.

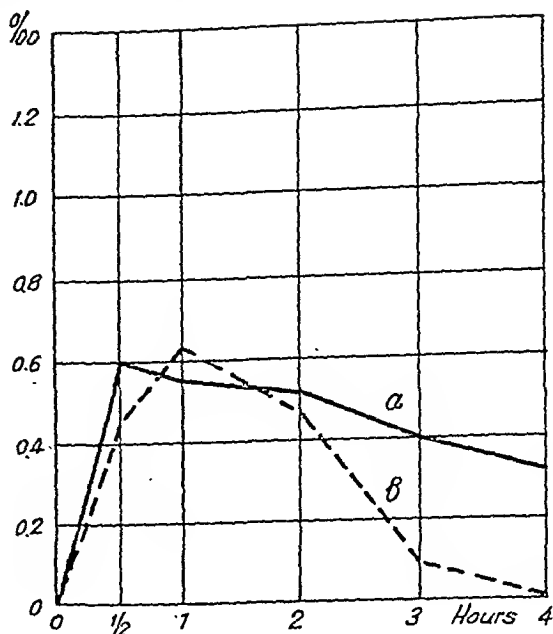


Fig. 4.

days ago she had a 2nd degree burn, for which she had received an injection of antitetanic serum, in addition to the other treatment. Five days after the injection she had fever (39.5°C) and two hours later, a papular eruption appeared, accompanied by unbearable pruritus. Blood pressure 9.5/6 cm Hg. Pulse rate 124/min. Laboratory examinations were negative. Blood eosinophils: 3 %. Curve «a» (fig. 4) was obtained when the eruption was at its highest intensity, curve «b» after it subsided. Although the initial part of curve «a» was of normal height, the final one was obviously higher.

Summary and Conclusions.

It became evident from the above description that in allergic conditions the alcoholemic curve is higher than the normal: the RES is functionally impaired.

In 9 out of the 14 tested patients, the alcoholemic curve was high, from the beginning to the end (see fig. 1 and 2). However, in 5 cases the curve was high during its final part, while the initial part was of normal height or slightly above it. This last type of curve was for the first time observed in these patients; it is difficult to explain this configuration.

The alcoholemic curve determined during the allergic reaction was found higher than the normal in 2 of our patients, in spite of the fact that they were feverish. According to the experiments of the first of us, the RES is hyperfunctioning when the temperature rises and the metabolic rate for the alcohol is found increased by 100 %. On the opposite, in another case of chronic urticaria without fever, where fever was induced by intravenous injection of typhoid vaccine, the alcoholemic curve taken during the induced fever was much lower than the normal. This means that the condition of the RES is different in cases with continuous fever due to the disease and in cases where fever was induced for therapeutic purposes.

The anti-histaminic drugs do not alter the configuration of the alcoholemic curve. We are of the opinion that this should be expected, for these drugs act on the histamin-like substances, which again act on the sensitized tissue, not on the RES.

1/2 hour after the administration of the alcohol, the eruption of the urticaria started subsiding. Six hours later, the eruption reached again its previous or sometimes even greater intensity. Is this due to the well-known action of the alcohol on the peripheral vessels, or to its action on the histamin-like substances, or to the modification of the RES-reaction? This cannot be answered easily.

The intoxication caused by the alcohol was of moderate intensity when the patients were in allergic reaction. Nevertheless, it was more marked than the one observed when the patients were cured from allergy. This can be easily explained, since the alcohol metabolism was slowed when the patients were in allergic reaction and consequently the central nervous system was under the influence of an increased quantity of alcohol.

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Studies on the Alcohol's Metabolism in Patients with Atrophic Liver Cirrhosis.

By

E. DANOPOULOS, K. MARATOS AND J. LOGOTHETOPOULOS.

(Submitted for publication October 5, 1953.)

The participation of the liver in the alcohol's metabolism was first demonstrated by Fiessinger (1) and his co-workers (1936). The experiments were made on dog livers with artificial circulation of oxygenated blood from the same animal. A part of the alcohol added to the blood was burned by the liver and its total amount was found to be reduced. In 1937, the Italians Seriani and Lolli (2) checked the alcohol's metabolism by taking the alcoholemic curves in patients with liver cirrhosis, after giving them 0.50 cc of alcohol per kg of body weight. Their experiments were performed in fasting patients and a few days later they were repeated 1—2 hours after a mixed diet's meal. The curves obtained did not show any difference from the normal, if the patients were fasting. Where the curves were taken 1—2 hours after a meal, the difference from the normal curve was evident. In these cases the alcoholemic curve was found higher than the normal (the curves taken in healthy individuals after a meal, are known to be 50—60 % lower). According to the authors, an alcoholemic curve taken after a meal can be used to test the liver's function.

One year later (1938) Ernteman and Heeres (3) published a relative study, having determined the alcoholemic curves in several patients and in liver diseases also; they were administering the alcohol in fasting patients only. These authors found an obviously higher curve, even in cirrhosis, which is contrary to the findings of Seriani and Lolli. Unfortunately, Ernteman and Heeres were administering such a small quantity of alcohol (0.20 cc, 96°, per Kg of body weight) that the configuration of the curves was subject to the inevitable mistakes, that are common to every micro-method. According to our experience on the matter, this mistake makes their conclusions doubtful.

At this same time (1938—1939), the first of us published his experimental studies (4, 5, 6, 7) a summary of which is given in the first part of these series.

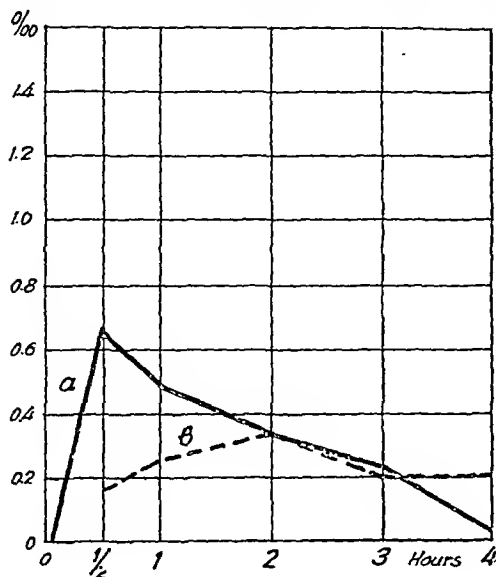


Fig. 1.

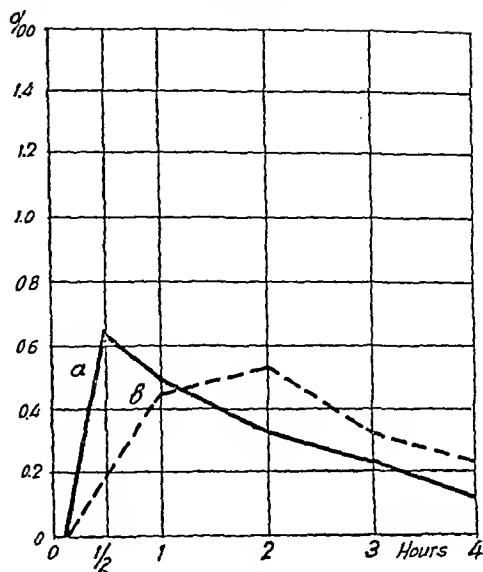


Fig. 2.

It was demonstrated that alcohol is burned mainly in the reticuloendothelial system. At first sight, our findings were not contrary to those of Seriani and Lolli (2). Since the liver cell itself is of no importance to the alcohol's metabolism, it seems reasonable that the alcoholemic curve in fasting cirrhotic patients would be almost normal.

However, our studies on the alcohol's metabolism in patients with undernutrition showed a higher curve in cachexia due to undernutrition. The curve was becoming higher, when cachexia was progressing. The impairment of the alcohol's metabolism was even more obvious in patients with oedema due to undernutrition. In the oedematic fluid considerable quantities of alcohol were found. These findings brought up the question, whether the conclusions of Seriani and Lolli were corresponding to the facts, being given that the quantity of alcohol in the ascitic fluid was not determined. Since the alcohol diffuses from the circulating blood into this fluid, there were not many doubts that the subject needed further investigation. The results of this investigation are reported here.

10 patients with liver cirrhosis were used, 7 males and 3 females, aged 17—70 years. 6 of them died in the Clinic. Probable etiologic factors of the disease were thought to be the following: moderate use of alcoholic drinks in 2 cases, abuse of drinking in 2, malaria and moderate drinking in 3, malaria only in 1 and none in 2. In one case the liver was palpable four fingers below the right costal margin. The autopsy of this case showed atrophic liver cirrhosis with two echinococcus cysts at the base. The spleen was palpable 3—10 fingers below the left costal margin in 9 out of the 10 cases. Ascites was always prominent and we were frequently obliged to empty the peritoneal cavity, obtaining by puncture big amounts of fluid (7—14 kg). The fluid was proved to be a transudate in all cases.

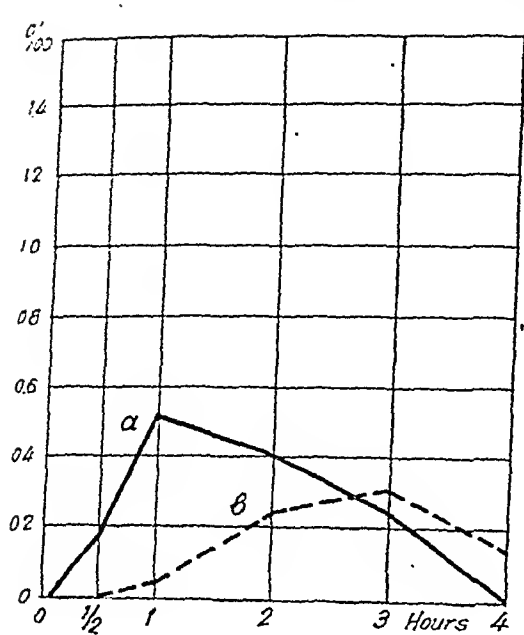


Fig. 3.

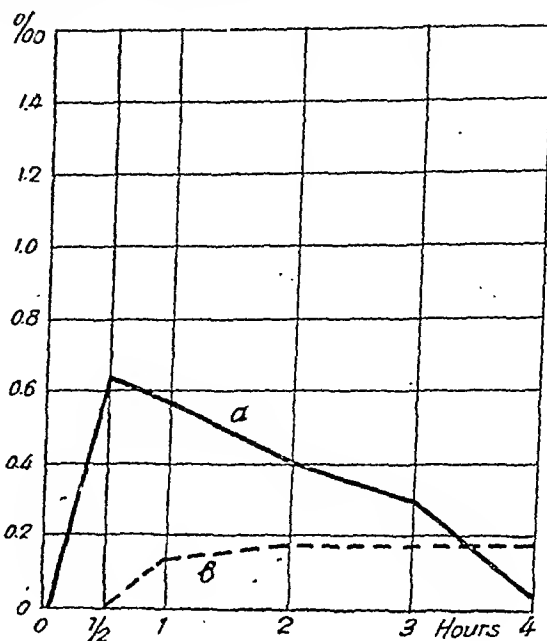


Fig. 4.

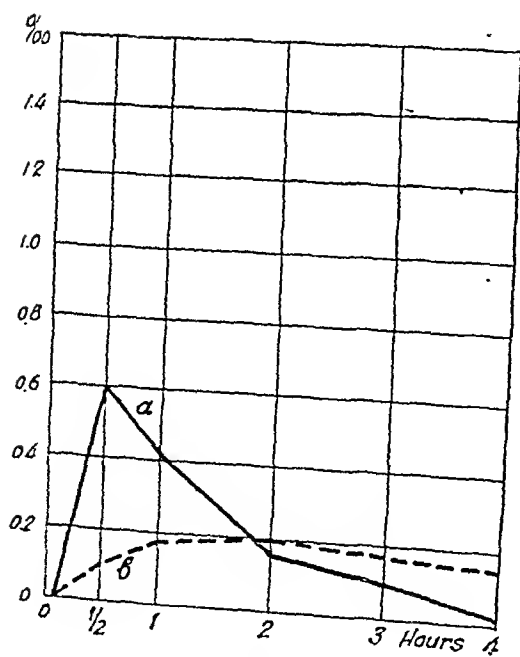


Fig. 5.

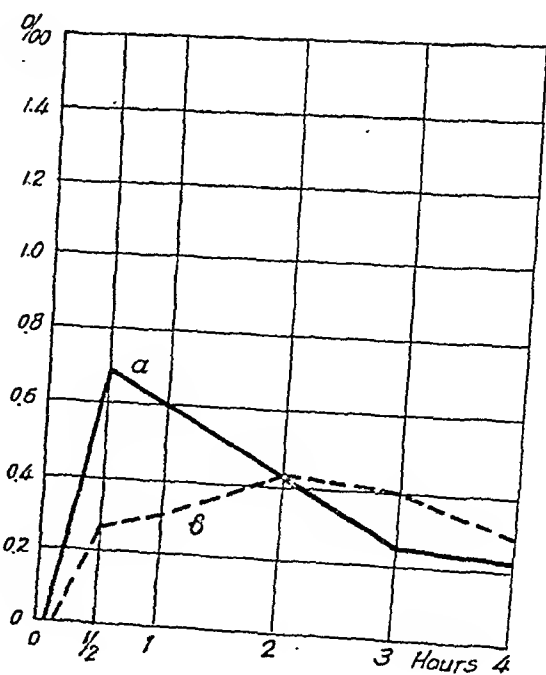


Fig. 6.

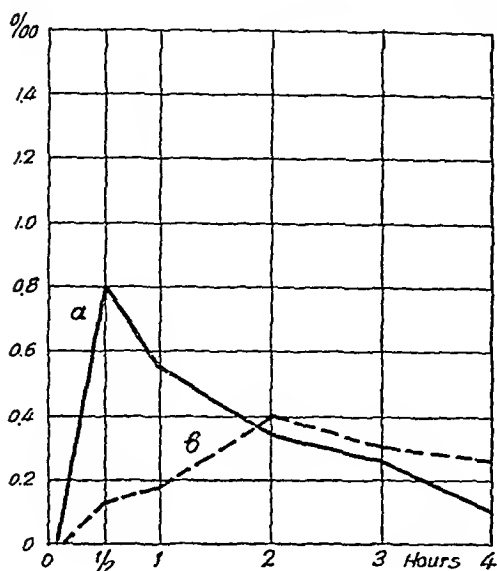


Fig. 7.

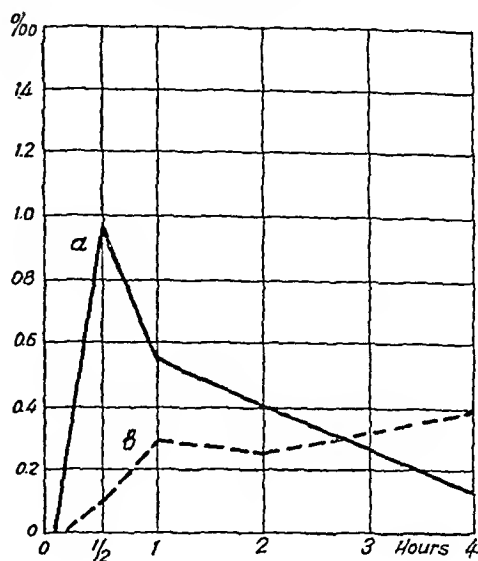


Fig. 8.

The cases were selected between the cirrhotic patients without any fever, since the experiments of the first of us (8) had shown that fever increases the alcohol's metabolism. 0.60 cc of alcohol per kg of body weight were given in the morning, to patients fasting for 12 hours. The real body's weight was considered, after omission of the varying weight of the ascitic fluid. The study of the alcohol's metabolism was done by following the quantity of alcohol in the blood and the ascitic fluid: small quantities of blood and fluid were obtained every half hour in the beginning and then every one hour, for 4 hours (s. fig. 1—10). In 5 of the cases, the amount of alcohol given per os was also injected into the peritoneal cavity, at least 7 days after the first experiment (s. fig. 11—15).

It should be noticed that the signs of the alcohol intoxication observed in these patients were rather mild; even milder than those observed in healthy individuals. On the opposite, in patients with undernutrition the intoxication was more evident than in healthy persons receiving the same amount of alcohol. The signs were almost insignificant, when the alcohol was injected into the peritoneal cavity. This will be explained below.

Analysis of the curves. Analysing thereafter the obtained alcoholemic curves, we start with these taken when the alcohol was given per os (fig. 1—10). Alcohol is rapidly absorbed by the gastro-intestinal tract, it enters the circulation and disperses into the interstitial fluids of the body, to be absorbed by the cells. The height and length of the alcoholemic curve «a» depends on the velocity with which alcohol is burned in the tissues. Naturally, the alcohol in our cases was also diffused into the ascitic fluid, which was always abundant, *i. e.* over 10 kgs, since our punctures were giving 7—12—14 kgs each time. The quantity of alcohol into the peritoneal fluid was shown in curve «b». Nevertheless, the total amount of alcohol

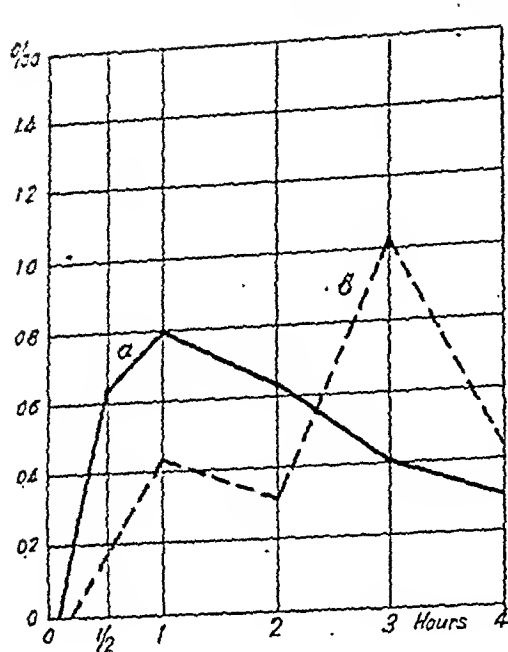


Fig. 9.

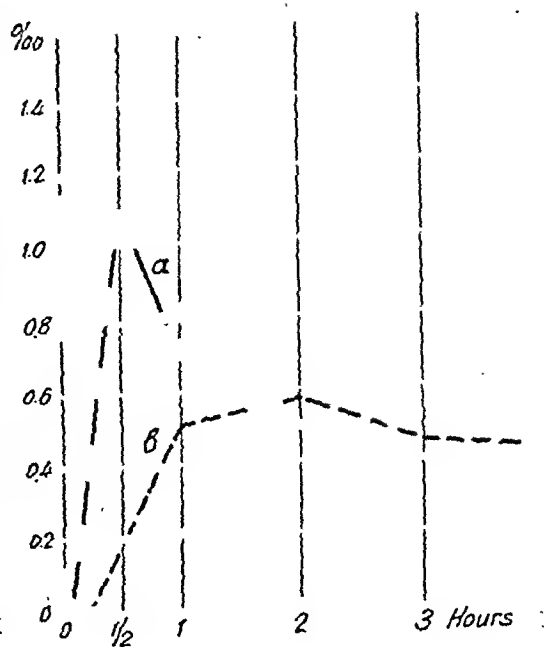


Fig. 10.

in the ascitic fluid was greater, for the quantity of the fluid was twice or more the volume of the blood. If we examine now the alcoholemic curve alone, we see that it is normal in the first 6 cases (fig. 1—6). In our 7th (fig. 7) and 8th (fig. 8) case it differs slightly from the normal; in the 9th (fig. 9) there is some difference in the initial height only and not in the duration and the final fall. It was only in the 10th case (fig. 10) that the curve was much higher than the normal, in its beginning and the end too. Up to this point our findings are the same with these of Seriani and Lolli (2). However, the normal or almost normal configuration of the curve does not necessarily mean a normal metabolism of the alcohol, for a big amount of it is found into the peritoneal fluid, as curve «b» shows. The amount of alcohol in the ascitic fluid gradually increases and 2 hours later (in one case earlier, in 2 cases later) it reaches the blood curve, which is meanwhile going down. The curves cross each other, and from this point, curve «b» is more or less higher than «a». Curve «b» goes down, that is, the amount of alcohol in the ascitic fluid is gradually reduced, since it is gradually absorbed by the peritoneum and either given back to the circulating blood in some proportion by the endothelial cells of the peritoneum. The percentage of alcohol in the ascitic fluid and consequently the height of curve «b» will obviously depend on the total amount of this fluid, at the time that the experiment was done. On the other side, the vascularisation of the peritoneum and its alterations, being different in each patient will naturally impair the height and configuration in general of curve «b», depending on the easier or more difficult diffusion of alcohol from the blood into the peritoneal fluid. Finally, the ability of the reticuloendothelial system in general, to burn the alcohol, depends on the seriousness of the patients' condition and influences the configuration of curve «a» and «b». Thus we can explain the rather minor differences from

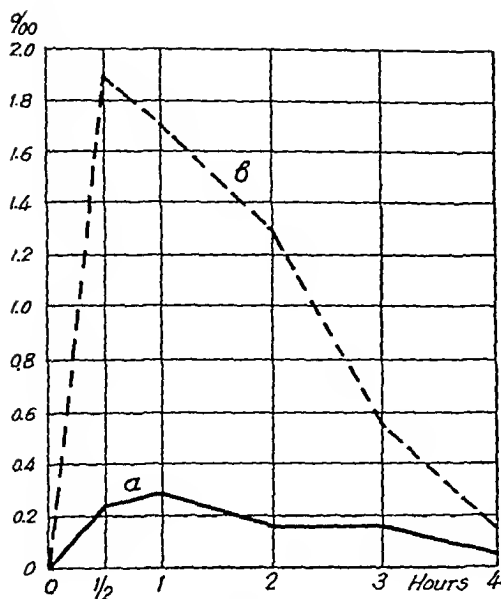


Fig. 11.

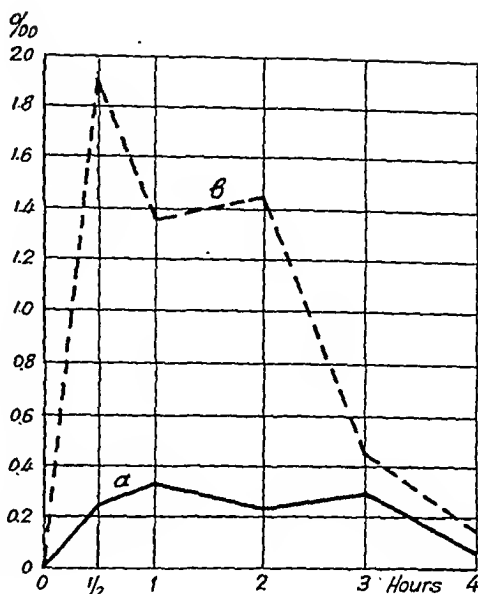


Fig. 12.

one case to the other, as far as curve «b» of the first 8 cases is concerned. There is a strange and inexplicable peak in the curve «b» of the 9th case, between the 2nd and 3rd hour. In the 10th case both curves are going high. This phenomenon had been observed by the first of us in experiments on rabbits, and by the first and second of us in men during undernutrition; it characterizes a very serious condition, for it shows the inability of the reticuloendothelial system to burn the alcohol, which means that it is in bad condition. In fact, the patient of this case died 7 days after the experiment.

Let us consider now the alcohol's metabolism after its intraperitoneal administration. Curve «b» shows here also the quantity of alcohol per kg of ascitic fluid, curve «a» its quantity in the blood. The alcohol is rapidly absorbed by the peritoneum after the injection, and is given to the whole organism by the portal vein and the greater circulation; on the other side its metabolism starts in the reticuloendothelial cells of the peritoneum. The prompt fall of curve «b» shows the rapid absorption by the peritoneum. It should be noticed that after the first 4 hours, only a small amount of alcohol was left in the ascitic fluid and the blood of the first two cases (fig. 11—15)¹, in spite of the fact that the alcohol was injected into the peritoneal cavity, the peritoneum was not quite normal and there was a portal stasis. In the third case (fig. 13) a bigger amount of alcohol is found on the fourth hour; it should be kept in mind though, that even at the beginning, in the first 30 minutes after the alcohol's injection, curve «b» is also high enough.

¹ Fig. 11—15 show the quantity of alcohol in the blood (curve «a») and the ascitic fluid (curve «b») after intraperitoneal administration. As shown in fig. 11 and 12, the alcohol was completely metabolized in 4 hours and curves «b» are finally falling. In fig. 13, curve «b» is not quite falling. The fall of curve «b» is greatly impaired in fig. 14 and 15. Curve «a» is obviously very low in all these diagrams.

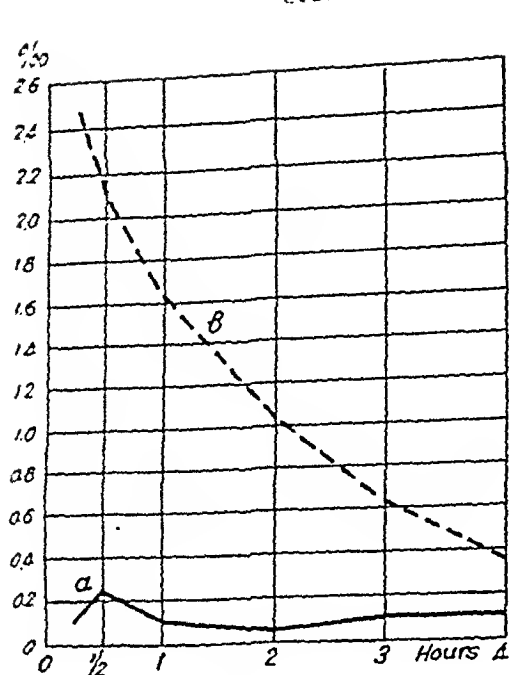


Fig. 13.

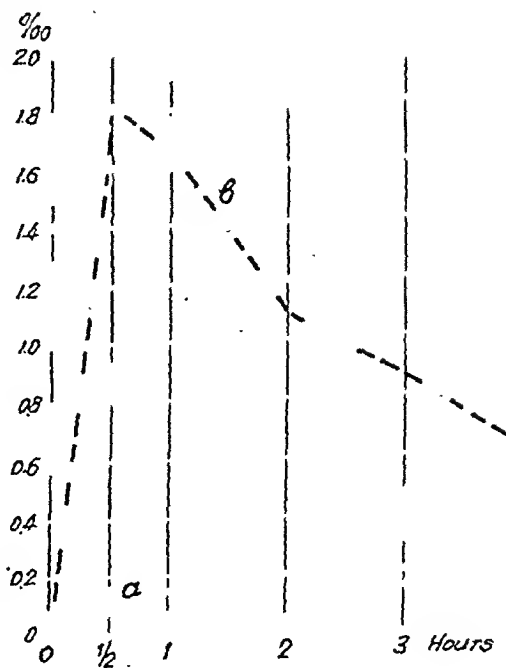


Fig. 14.

In the last two cases (fig. 14 and 15) curve «b» stays high enough, even during the fourth hour. Is this due to a slowed absorption rate or to an impairment of the organism's ability to burn the alcohol? If we follow the fall of curve «b» during the first two hours, we will remark that it is normal. It slows down during the last two hours. We could conclude out of this, that the absorption is normal but the ability of the «tired» reticuloendothelial system to burn the alcohol, is affected as it usually happens in similar cases, when the alcohol is given by mouth. If on the opposite, the absorption is normal and the reticuloendothelial system burns the alcohol slowly, why the quantity of alcohol in the blood does not increase, in which case the curves would approach each other? It comes out, therefore, that due to unknown factors the absorption is normal at the beginning and then it is gradually slowed.

It is difficult to state, to what extent the local metabolism of the alcohol by the endothelial cells of the peritoneum can account for the difference in the configuration of the curves. It is easily understood on the other side, why the intoxication signs were so mild in these patients: the peripheral cells and consequently the cerebral cells imbibed the alcohol at a moderate or small degree; a great part of it remained in the peritoneum in the first series, when it was given by mouth, but especially in the second series, when injected into the peritoneal cavity.

Conclusions and Summary.

1. The alcohol's metabolism in patients with atrophic liver cirrhosis is impaired to several extent in several cases, although the configuration of the curves is usually normal.

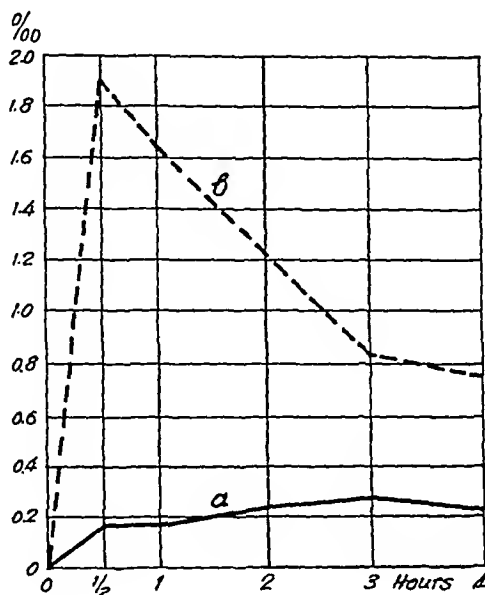


Fig. 15.

2. The normal configuration of the alcoholemic curve, which is usually found, is due to the fact that a certain quantity of alcohol diffuses into the ascitic fluid, wherefrom it is absorbed by the peritoneum and brought back to the circulating blood and through it to the whole organism, to be burned.

3. A great impairment of the alcohol's metabolism, leading to high curves (as in fig. 10) means an obvious dysfunction of the reticuloendothelial system and therefore a pre-mortal condition.

4. The intraperitoneous injection of alcohol leads to a relatively quick absorption and a fall of the curves within 4 hours, like when it is given per os. This does not happen always. What hinders the absorption in some of the cases, is not made clear from these experiments.

5. The diffusion of a certain amount of alcohol into the ascitic fluid and its gradual re-entrance from there into the circulation, can account for the appearance of intoxication signs that are milder than those expected from the amount of alcohol administered.

Literature.

1. Fiessinger, N., Benard, H., Courtial, I., and Dermer, L.: C. r. Soc. Biol. Paris 122, 1255—1258 (1936). — 2. Seriani, E., and Lolli: Fisiol. e Med. 8, 1—15 (1937). — 3. Ernteman, I., and Heeres, P.: Acta Med. Scand. vol. XCVI, fasc. II—IV, 198—216. — 4. Danopoulos, E.: Zeitschr. f. d. ges. exp. Med. 103, 212—221 (1938). — 5. Danopoulos, E.: Zeitschr. f. d. ges. exp. Med. 106, 374—376 (1939). — 6. Danopoulos, E.: Zeitschr. f. d. ges. exp. Med. 106, 396—400 (1939). — 7. Danopoulos, E.: Zeitschr. f. d. ges. exp. Med. 106, 401—405 (1939). — 8. Danopoulos, E.: Zeitschr. f. d. ges. exp. Med. 106, 406—408 (1939).

Book Reviews.

V. E. Brown: Synopsis of Medical Entomology. Lithoprinted in U. S. A., Edward Brothers, Inc., Ann Arbour, Michigan 1953. 219 pp. 136 fig.

This excellent and really needed book is dedicated to the author's students and colleagues and to those who are interested in public health work and insect control everywhere.

The book begins with a classification of the arthropoda, contains 31 chapters, and deals with scorpions, spiders, ticks, mites, centipedes, millipedes, crustacea — of which many are intermediate hosts of parasitic helminthes — flies, gnats, mosquitoes, sand flies, tsetse flies, fleas, lice etc.

The author is Assistant Professor of Biology at Marquette University and former Captain Sn. C., Medical Department, U. S. Army. He seems to have great experience in the field of medical entomology. Especially for medical men practising in foreign parts of the world this book is of inestimable value.

I. Holmgren.

A Ciba Foundation Colloquia on Endocrinology. Vol. VII. Synthesis and Metabolism of Adrenocortical Steroids. J. and A. Churchill, Ltd., London 1953. 297 pp. and 29 illustrations. Price 30 s. net.

The seventh volume of the Ciba Foundation Colloquia on Endocrinology deals with two very important aspects of experimental endocrinology that are of current interest. Interest in the steroid hormones was aroused in the early 'thirties when the chemical relationship of the gonadal hormones to the steroids became apparent. The biological importance of the steroid hormones was quickly realized, and much work has been done to elucidate their biochemistry. The dramatic results in the relief of rheumatoid arthritis with cortisone, reported by the Mayo Clinic group in 1948, provided the greatest stimulus hitherto for enterprise in exploring other practical possibilities of endocrinology. The present volume deals with the latest advances in the elucidation of the metabolism of the adrenocortical steroids and their preparation by synthesis.

The first section of the book, consisting of twelve chapters, treats of the synthesis of adrenocortical steroids from a variety of starting materials. It is beyond the scope of the reviewer to give a critical evaluation of this section. The last section of the book, consisting of eight chapters dealing with the metabolism of the adrenocortical steroids, is of greater interest to biochemists and endocrinologists. Five of these chapters report the outstanding work in this field being done by Pincus, Hechter, Dorfman and their associates in the biochemical laboratory of the Worcester Foundation at Shrewsbury, Massachusetts. Of special interest is the chapter by Hechter in which he gives an account of the attempts made to elucidate the biogenesis of the adrenal cortical hormones with radioactive cholesterol and other labelled compounds, principally the carbon-2 fragments. The experiments were carried out on the isolated perfused adrenal and liver of different animal species. The author has tentatively constructed a scheme of corticosteroidogenesis in which cholesterol is assumed to be the main steroid precursor. Furthermore, it is shown that the action of the adrenocorticotrophic hormone is on the initial phase of corticoidogenesis and not on the final phase involving the conversion of progesterone into different adrenocortical steroids.

Also of interest is the outstanding work done by Samuels and Dorfman and his co-workers on a new aspect of steroid biochemistry, the enzyme systems involved in adrenocortical steroid metabolism. The chapters by Pincus and his co-workers on corticosteroid metabolism in man and by Morris and his associates on the estimation of the individual adrenocortical hormones in the human peripheral blood will be of interest to research workers in clinical endocrinology.

On the whole the book is of little help to the clinician, but to all interested in the expanding field of experimental endocrinology it will be of great value. Important advances in this fundamental field can be expected within the next few years.

Rolf Luft.

Publications Received.

Redaktionen sänder på anmodan böcker för recension.

- Dapim Refuim* (Medical Quarterly), No. 4, Tel-Aviv, 1953.
- Chronique de l'organisation mondiale de la santé*. Vol. 8, No. 1, Genève, 1954.
- Aldo Castellani: Persistency of some important cultural and biochemical characters of certain intestinal bacteria isolated two, three and over four decades ago. *Giornale di Batteriologia e Immunologia*, Torino, Italia, 1954.
- E. Ashworth Underwood: Pharmacy and therapeutics in the age of Elisabeth I. 18 pp. Price: 2s. 6d. The Pharmaceutical Press, London W. C. 1, 1954.
- The Gunma Journal of Medical Sciences*. Vol. II, No. 3, Maebashi, Japan, 1953.
- Forhandlinger i Den Norske Lægeforenings* 32. landsmøte 20. og 21. august 1953 og *Forhandlinger i Den norske Lægeforenings landsstyremøte* 22. august 1953, Oslo.
- La Revue du Praticien*, Tome III, no. 24 et 26, Paris, 1953.
- Ciba Foundation Symposium. *The Chemical Structure of Proteins*. By G. E. W. Wolstenholme. 222 pp. 49 ill. Price: 25s. net. J. & A. Churchill Ltd., London W. 1, 1954.
- Förteckning över filmer tillgängliga i *Societas Medica Scandinavica's arkiv* 1954. Med. Högskolans bibliotek, Göteborg, 33.
- Helmut Gillmann: Einführung in die vektorielle Deutung des EKG. 106 S. 83 Abb. Preis: brosch. DM 19.—, geb. DM 21.—. Verlag Dr. Dietrich Steinkopff, Darmstadt, 1954.
- Ciba Foundation Symposium. *Peripheral Circulation in Man*. By G. E. W. Wolstenholme and Jessie S. Freeman. 219 pp. 72 ill. Price: 25s. net. J. & A. Churchill Ltd., London W. 1, 1954.
- Ultrasonic and Ultrashort Waves in Medicine*, by Johanna M. van Went. 384 pp. Elsevier Publishing Company, Amsterdam, 1954. Price: 52/6 fl.
- Memorie scientifiche dedicate a Vito Maria Buscaino nel XXV anno del suo insegnamento*. 544 p. Quaderni di *Acta Neurologica*, III, Napoli, 1953.
- El Torax*, Vol. II, No. 3, 1953. V Congreso Uruguayo de la Tuberculosis. Montevideo.
- Third Annual Report on Stress*, by Hans Selye and Alexander Horava. 637 pp. Acta, Inc., Medical Publishers, Montreal, Canada, 1954.

- The Mechanism of Inflammation.* An International Symposium. Edited by G. Jasmin and A. Robert. 308 pp. Acta, Inc., Medical Publishers, Montreal, Canada, 1954.
- To the Memory of Torsten Thunberg.* Acta Physiologica Scandinavica, Vol. 30, Suppl. 111, Lund, 1953.
- In Honour of S. Ramón y Cajal on the centenary of his birth 1952.* Acta Physiologica Scandinavica, Vol. 29, Suppl. 106, Stockholm, 1953.
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